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(54) Title: CHEMICAL COMPOUNDS

(57) Abstract

The invention relates to masked monophosphate nucleoside analogues, their preparation and their therapeutic use in the treatment of viral infection, including infection by HIV. In particular, the invention relates to aryl phosphoramidate 2',3'-dideoxy and 2',3'-dideoxydidehydro nucleoside analogues and of PMEA.

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CHEMICAL COMPOUNDS

The present invention relates to a new class of nucleoside analogues and their therapeutic use in the prophylaxis and 5 treatment of viral infection, for example by human immunodeficiency virus (HIV), which is believed to be the aetiological agent in human acquired immunodeficiency syndrome (AIDS).

10 There has been much interest in the use of nucleoside analogues as inhibitors of HIV. 2',3'-dideoxy-2',3'-didehydrothymidine (d4T) and 3'-azido-3'-deoxythymidine (AZT) are both known inhibitors of HIV [Hitchcock et al., Antiviral Chem. Chemother. (1991), 2, 125; Mansuri et al., 15 Antimicrob. Agents Chemother., (1990), 34, 637.]. The inhibition of HIV by these, and other nucleoside analogues, is conventionally thought to depend upon conversion of the nucleoside analogue *in vivo* to the corresponding 5'-triphosphate by (host-cell) kinase enzymes. However, this 20 absolute dependence upon (host-cell) kinase-mediated activation can lead to poor activity, the emergence of resistance, and clinical toxicity.

In order to reduce the dependence on kinase enzymes the use 25 of masked phosphate pro-drugs of the bioactive nucleotide forms of several chemotherapeutic nucleoside analogues has been suggested [McGuigan et al., Nucleic Acids Res., (1989), 17, 6065; McGuigan et al., *Ibid.*, (1989), 17, 7195; Chawla et al., J. Med. Chem., (1984), 27, 1733; Sergheraert et al., 30 J. Med. Chem. (1993), 36, 826-830.]. In particular, McGuigan et al [J. Med. Chem. 36, 1048-1052 (1993)] have reported the preparation of aryl ester - phosphoramidate derivatives of AZT. In vitro evaluation of these compounds revealed the compounds to have anti-HIV activity. However, 35 in "normal" thymidine kinase rich (TK⁺) cells, the activity of such compounds was at least an order of magnitude less than the parent nucleoside AZT. Only in TK-deficient (TK⁻) cells, in which the activity of the aryl ester -

phosphoramidate derivatives was virtually maintained but the activity of AZT was reduced, did the activity of the derivatives exceed that of AZT.

5 McGuigan *et al* [Bioorganic & Medical Chemistry Letters, 3(6), 1203-1206 (1993)] have also reported preparation of triester phosphate derivatives of d4T. Again, *in vitro* evaluation of these compounds revealed that whilst the compounds have significant anti-HIV activity, the activity 10 is less than that of the parent nucleoside d4T in TK⁺ cells.

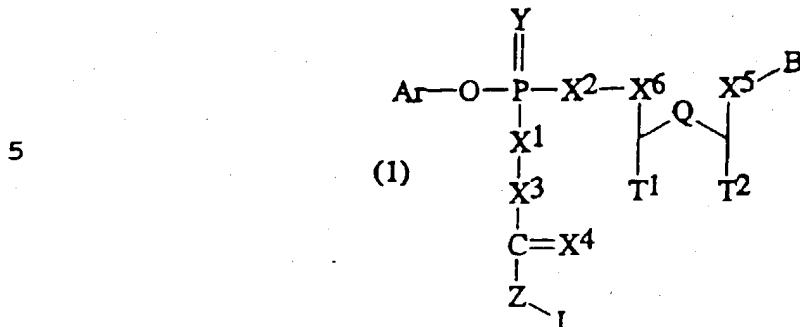
Abraham and Wagner (Nucleosides and Nucleotides 13(9). 1891-1903 (1994)) have reported the preparation of nucleoside phosphoramidate diesters and triesters but do not report any 15 biological activity.

The acyclic nucleoside analogue 9(2-phosphonomethoxyethyl) adenine (PMEA), and analogues thereof, have been demonstrated to show activity against herpes viruses and 20 retroviruses including HIV (Calio *et al.*, Antiviral Res., (1994), 23(1), 77-89; Balzarini *et al.*, AIDS, (1991), 5(1), 21-28).

To date, the approach of providing masked phosphate pro-25 drugs has failed to enhance the anti-viral activities of the parent nucleoside analogues such as AZT and d4T in TK⁺ cells. Furthermore, the emergence of resistance to the nucleoside analogues in their bioactive 5'-triphosphate form has rendered the reported masked phosphate pro-drugs and 30 their parent nucleoside analogues potentially ineffective.

It has now been found that a particular class of masked nucleoside analogues are highly potent viral inhibitors in both TK⁻ and TK⁺ cells, and yet retain activity against 35 nucleoside (e.g. d4T) - resistant virus.

According to the present invention there is provided a compound of the formula (1)



10 wherein Ar is an aryl group;

Y is oxygen or sulphur;

15 X¹ is selected from O, NR³, S, CR³R⁴, CR³W¹ and CW¹W² where R³ and R⁴ are independently selected from hydrogen, alkyl and aryl groups; and W¹ and W² are heteroatoms;

20 X²-X⁶ may be absent; or X⁶ is CH₃ and X² is selected (independently of X¹) from O, NR³, S, CR³R⁴, CR³W¹ and CW¹W² where R³ and R⁴ are independently selected from hydrogen, alkyl and aryl groups; and W¹ and W² are heteroatoms;

25 X³ is a C₁₋₆ alkyl group;

X⁴ is oxygen or CH₂;

30 X⁵ may be absent or is CH₂;

Z is selected from O, NR⁵, S, alkyl and aryl groups, where R⁵ is selected from hydrogen, alkyl and aryl groups;

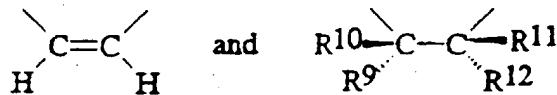
35 J is selected from hydrogen, alkyl, aryl, heterocyclic and polycyclic groups;

Q is selected from O, NR⁶, S, CR⁶R⁷, CR⁶W³ and

CW^3W^4 , where R^6 and R^7 are independently selected from hydrogen, alkyl and aryl groups; and W^3 and W^4 are heteroatoms;

5 T^1 and T^2 are independently selected from hydrogen and CH_2R^8 , where R^8 is selected from H, OH and F; or T^1 and T^2 are linked together and together are selected from the groups

10



15

where R^9 is selected from H, halogen, CN, NH_2 , CO-alkyl and alkyl; and R^{10} , R^{11} , R^{12} are independently selected from H, N, halogen, CN, NH_2 , CO-alkyl and alkyl;

20

B is a purine or pyrimidine base;

or a pharmaceutically acceptable derivative or metabolite thereof.

25

The compounds of the present invention are potent anti-viral agents. In particular, they are highly active against HIV in both TK and TK⁺ cells. Particularly surprising is the activity of the compounds of the present invention against 30 nucleoside-resistant HIV. These observations indicate that the activity of these compounds is not wholly dependent upon the conventional mode of action (requiring hydrolysis of the phosphate aryl ester and P-X¹ bonds followed by kinase-dependent conversion to the 5'-triphosphate derivative), but 35 arises from an entirely different mode of action. The experimental data presented herein indicates that the compounds and metabolites of the present invention are directly acting as reverse transcriptase (RT) inhibitors via

a previously unrecognised metabolic pathway and mechanism of action.

Reference in the present specification to an alkyl group means a branched or unbranched, cyclic or acyclic, saturated or unsaturated (e.g. alkenyl or alkynyl) hydrocarbyl radical. Where cyclic, the alkyl group is preferably C₃ to 5 C₁₂, more preferably C₃ to C₁₀, more preferably C₃ to C₇. Where acyclic, the alkyl group is preferably C₁ to C₁₆, more preferably C₁ to C₆, more preferably methyl. Reference in the present specification to alkoxy and aryloxy groups means alkyl-O- and aryl-O- groups, respectively. Reference to 10 alkoyl and aryloyl groups means alkyl-CO- and aryl-CO-, respectively.

Reference in the present specification to an aryl group means an aromatic group, such as phenyl or naphthyl, or a 15 heteroaromatic group containing one or more, preferably one, heteroatom, such as pyridyl, pyrrolyl, furanyl and thiophenyl. Preferably, the aryl group comprises phenyl or substituted phenyl.

20 The alkyl and aryl groups may be substituted or unsubstituted, preferably unsubstituted. Where substituted, there will generally be 1 to 3 substituents present, preferably 1 substituent. Substituents may include halogen atoms and halomethyl groups such as CF₃ and CCl₃; oxygen 25 containing groups such as oxo, hydroxy, carboxy, carboxyalkyl, alkoxy, alkoyl, alkoyloxy, aryloxy, aryloyl and aryloyloxy; nitrogen containing groups such as amino, alkylamino, dialkylamino, cyano, azide and nitro; sulphur containing groups such as thiol, alkylthiol, sulphonyl and 30 sulphoxide; heterocyclic groups which may themselves be substituted; alkyl groups, which may themselves be substituted; and aryl groups, which may themselves be substituted, such as phenyl and substituted phenyl. Alkyl includes substituted and unsubstituted benzyl.

Reference in the present specification to heterocyclic groups means groups containing one or more, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, 5 pyrazolidinyl, tetrahydrofuranyl, pyranyl, pyronyl, pyridyl, pyrazinyl, pyridazinyl, piperidyl, piperazinyl, morpholinyl, thionaphthyl, benzofuranyl, isobenzofuranyl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolinyl, 7-azaindolyl, isoindazolyl, benzopyranyl, coumarinyl, isocoumarinyl, 10 quinolyl, isoquinolyl, naphthridinyl, cinnolinyl, quinazolinyl, pyridopyridyl, benzoxazinyl, quinoxadinyl, chromenyl, chromanyl, isochromanyl and carbolinyl.

References in the present specification to polycyclic groups 15 means a group comprising two or more non-aromatic carbocyclic or heterocyclic rings which may themselves be substituted.

Reference in the present specification to halogen means a fluorine, chlorine, bromine or iodine radical, preferably 20 fluorine or chlorine radical.

The group Ar comprises a substituted or unsubstituted aryl group, wherein the term "aryl group" and the possible substitution of said group is as defined above. Preferably, 25 Ar is a substituted or unsubstituted phenyl group. Particularly preferred substituents are electron withdrawing groups such as halogen (preferably chlorine or fluorine), trihalomethyl (preferably trifluoromethyl), cyano and nitro groups. Preferably, Ar is phenyl, 3,5-dichloro-phenyl, p-30 trifluoromethyl-phenyl, p-cyano-phenyl, or p-nitro-phenyl.

Y may be oxygen or sulphur. Preferably, Y is oxygen.

X¹ is from O, NR³, S, CR³R⁴, CR³W¹ and CW¹W² where R³ and R⁴ are 35 independently selected from hydrogen, alkyl and aryl groups; and W¹ and W² are heteroatoms. Preferably, X¹ is selected from O, S and NR³. Preferably, X¹ is NR³. When present, R³ is preferably H. When present, W¹ and W² may independently comprise any heteroatom such as a halogen, preferably

fluorine.

X^2-X^6 may be absent; or X^6 is CH_2 and X^2 is selected (independently of X^1) from O, NR^3 , S, CR^3R^4 , CR^3W^1 and CW^1W^2 5 where R^3 and R^4 are independently selected from H, alkyl and aryl groups; and W^1 and W^2 are heteroatoms. When present, X^2 is preferably oxygen. When present, R^3 is preferably H. When present W^1 and W^2 may independently comprise any heteroatom such as halogen, preferably fluorine.

10

X^4 is oxygen or CH_2 . Preferably, X^4 is oxygen.

X^5 may be absent or is CH_2 .

15 Z may comprise O, NR^5 , S, alkyl or aryl groups, where R^5 is selected from H, alkyl and aryl groups. Preferably, Z is O or NR^5 . Preferably, R^5 is hydrogen. Most preferably, Z is oxygen.

20 J is selected from hydrogen, alkyl, aryl, heterocyclic and polycyclic groups. Preferably, J is a substituted or unsubstituted alkyl group. Preferably, J is a substituted or unsubstituted C_{1-6} alkyl group, preferably a benzyl or methyl group.

25

X^3 is a C_{1-6} alkyl group. X^3 may be a C_{1-6} substituted or unsubstituted, branched or unbranched, methylene chain. Preferably, X^3 is a group CR^1R^2 where R^1 and R^2 are independently selected from hydrogen, alkyl and aryl groups.

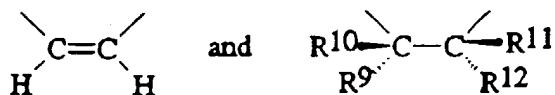
30 Preferably, at least one of R^1 and R^2 is hydrogen. It will be appreciated that if R^1 and R^2 are different, the carbon atom to which they are bonded is an asymmetric centre. The stereochemistry at this site may be R or S or mixed. When one of R^3 and R^4 is hydrogen, the stereochemistry is 35 preferably S.

Q is selected from O, NR^6 , S, CR^6R^7 , CR^6W^3 and CW^3W^4 , where R^6 and R^7 are independently selected from hydrogen, alkyl and aryl groups; and W^2 and W^3 are heteroatoms such as halogen

atoms, preferably fluorine. Preferably, Q is O, S, CH₂ or CF₂. Most preferably, Q is oxygen.

T¹ and T² are independently selected from hydrogen and CH₂R⁸ where R⁸ is selected from H, OH and F; or T² and T² are linked together and together are selected from the groups:-

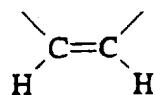
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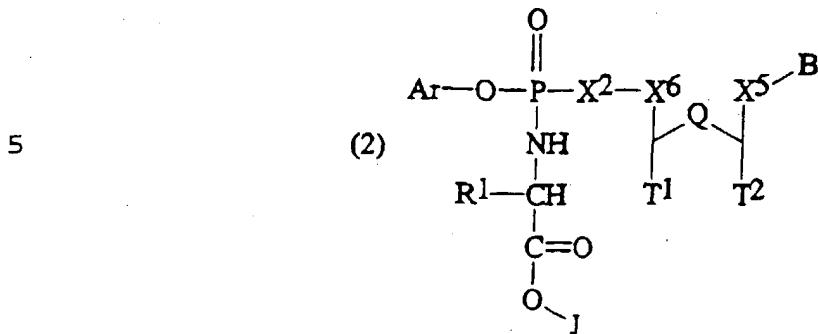
where R⁹ is selected from H, halogen, CN, NH₂, CO-alkyl, and alkyl, preferably R⁹ is H or F; and R¹⁰, R¹¹, and R¹² are independently selected from H, N, halogen, CN, NH₂, CO-alkyl, and alkyl, preferably R¹⁰, R¹¹ and R¹² are independently selected from H, F and N₃. It will be appreciated that R⁹ corresponds to the 3' - α position and R¹⁰ corresponds to the 3' - β position. Preferably, T¹ and T² are linked together and together form the group:-

25



30 B comprises a purine or pyrimidine base, such as adenine thymine, uracil, cytosine or guanine and derivatives thereof. Derivatives thereof include substituted purine or pyrimidine bases wherein the substituents are as defined above. Examples of substituted bases include 5-substituted 35 pyrimidine. Preferably, B is adenine or thymine.

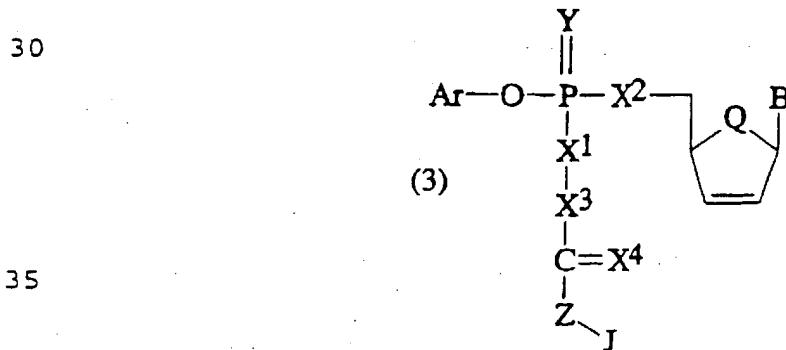
Preferably, the present invention provides a compound of formula (2)



10 wherein Ar, R¹, J, X², X⁵, X⁶, Q, T¹, T² and B are as defined above; or a pharmaceutically acceptable derivative or metabolite thereof.

15 It will be appreciated that the group -NH-CHR¹-CO₂J corresponds to a carboxy-protected α -amino acid. Preferably, the group R¹ corresponds to the side chain of a naturally occurring amino acid such as Alanine, Arginine, Asparagine, Aspartic Acid, Cysteine, Cystine, Glycine, Glutamic Acid, Glutamine, Histidine, Isoleucine, Leucine, 20 Lysine, Methionine, Phenylalanine, Proline, Serine, Threonine, Tryptophan, Tyrosine, Valine. Preferably, R¹ is Me or PhCH₃, corresponding to the side chain of alanine or phenylalanine, respectively. Preferably, the stereochemistry at the asymmetric centre -CHR¹- corresponds 25 to an L-amino acid.

According to one preferred embodiment, the present invention provides a compound of formula (3):-



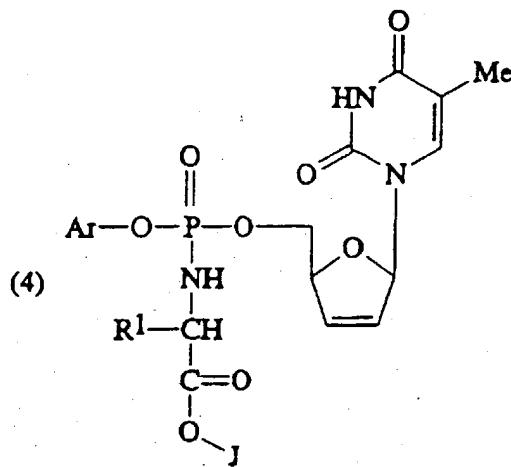
wherein Ar, Y, X¹, X², X³, X⁴, Z, Q and B are as defined above.

More preferably, the invention provides a compound, according to formula (3), of formula (4):-

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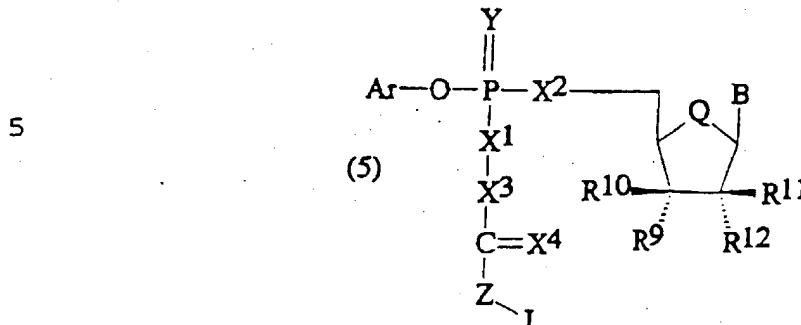
wherein Ar, R¹ and J are as defined above; or a pharmaceutically acceptable derivative or metabolite thereof. Preferably, the invention provides a compound of formula (4) in which Ar, R¹ and J are defined in accordance with Table 1.

Table 1

Compound Reference	Ar	R ¹	J
5 323	4-EtPh	Me	Me
324	Ph	Me	Me
327	4-FPh	Me	Me
526	3-CF ₃ Ph	Me	Me
546	3,5-Cl ₂ Ph	Me	Me
10 730	Ph	Me	Bzl
776	2,4-Br ₂ Ph	Me	Me
779	F ₃ Ph	Me	Me
862	Ph	Me	Hexyl
863	Ph	Bzl	Me
15 864	Ph	CH ₂ iPr	Me
865	Ph	iPr	Me
866	Ph	H	Me
867	Ph	[CH ₂] ₂ SMe	Me
868	2,4Br ₂ Ph	Me	Bzl
20 877	Ph	Bzl	Bzl
878	Ph	Bzl	tBu
892	Ph	Me	Cyclohexyl
893	Ph	Me	tBu
1078	Ph	CH ₂ CO ₂ H	Me
25 1214	Ph	CH ₂ CH ₂ CH ₂ NHC(NH ₂)NH	Me
1218	Ph	Me	n-Pent
1219	Ph	Me	neo-Pent
1226	Ph	Me	1-Naphthyl
1227	Ph	Me	2-Naphthyl

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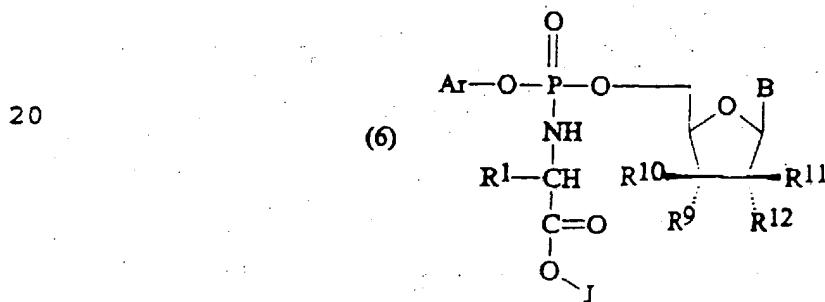
According to a further preferred embodiment, the present invention provides a compound of formula (5)



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wherein Ar, Y, X¹, X², X³, X⁴, Z, J, R⁹, R¹⁰, R¹¹, R¹², Q and B as defined above.

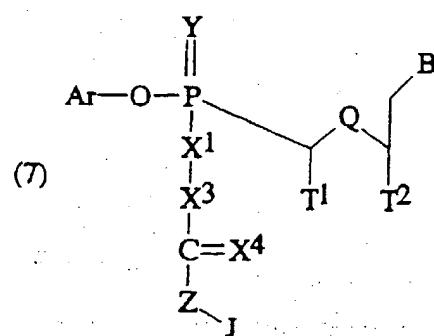
More preferably, the invention provides a compound,
15 according to formula (5), of the formula (6):-



25 wherein Ar, R¹, J, R⁹, R¹⁰, R¹¹, R¹² and B are as defined above.

According to a further preferred embodiment, the present invention provides a compound of formula (7):-

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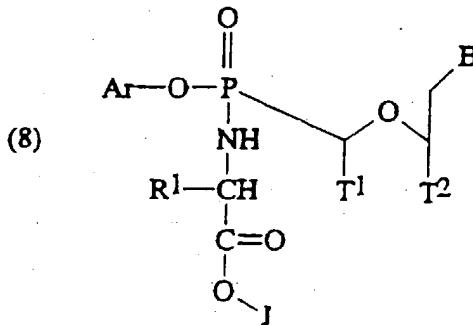
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wherein Ar, Y, X¹, X³, X⁴, Z, J, Q and B are as defined above and T¹ and T² are independently selected from H and CH₂R⁸ wherein R⁸ is as defined above. Preferably, B is a purine base. More preferably, B is adenine. Preferably, T¹ is 5 hydrogen. Preferably, T² is CH₂R⁸. These compounds are analogues of the acyclic nucleoside analogue 9-(2-phosphonylmethoxyethyl) adenine (PMEA), which has been demonstrated to show activity against herpes viruses and retroviruses (Calio *et al.*, *Antiviral Res.*, (1994), 23(1), 10 77-89; Balzarini *et al.*, *AIDS*, (1991), 5(1), 21-28).

More preferably, the invention provides a compound, according to formula (7), of formula (8):-

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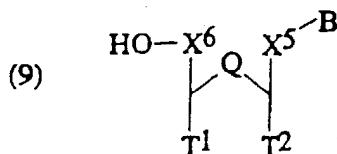


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wherein Ar, R¹, J, T¹, T² and B are as defined above.

It is a feature of the aryl ester phosphate compounds (1) of 30 the present invention that they exhibit significantly enhanced anti-viral efficacy, in both *in vitro* and *in vivo* tests, in comparison to their corresponding nucleoside analogue (9)

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In addition, the compounds of the present invention exhibit significantly reduced toxicity in comparison to their 5 corresponding analogue (9).

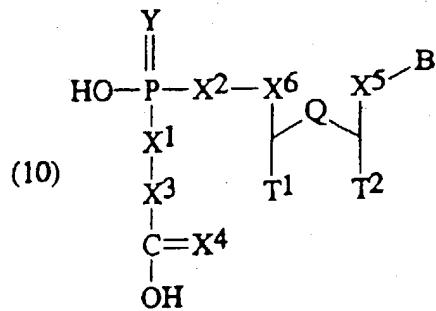
The compounds of the present invention thus exhibit a greatly enhanced selectivity index (ratio of CC_{50} (toxicity): EC_{50} (activity)) in comparison to their 10 corresponding nucleoside analogue.

Experiments with radiolabelled compounds of the present invention have shown that the compounds give enhanced intracellular levels of nucleoside 5'-triphosphate, the 15 enhancement being particularly significant in TK cells. Thus, the compounds of the present invention may act in part by the known metabolic pathway.

However, it has been found that the compounds of the present 20 invention show surprising activity against nucleoside resistant strains of HIV. This indicates that the compounds of the present invention are also acting by a pathway independent of a 5'-triphosphate metabolite.

25 It has been demonstrated that the compounds of the present invention lead to intracellular generation of high levels of a metabolite (10).

30

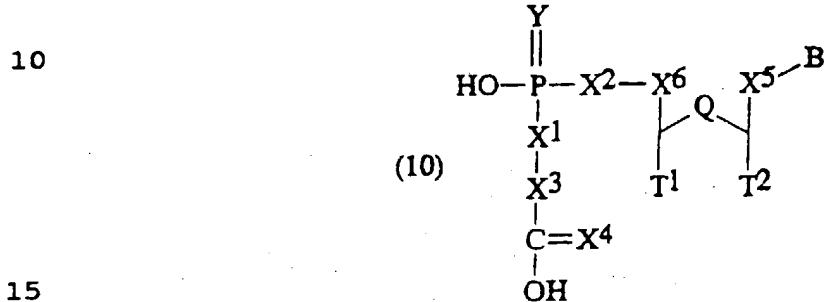


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Metabolite (10) may also be prepared by treatment of the corresponding compound according to formula (1) with hog

liver esterase. Moreover, it has been shown that compounds of formula (10) are direct inhibitors of reverse transcriptase from HIV.

5 According to a further aspect of the present invention there is provided a compound of formula (10)



wherein Ar, Y, X¹, X², X³, X⁴, X⁶, T¹, T², Q, X⁵ and B are as defined above, or a pharmaceutically acceptable derivative or metabolite thereof.

20 The intracellular generation of anti-viral metabolites such as (10) is an important feature of the invention for several reasons. Firstly, the direct activity of (10) on RT removes the necessity for further nucleotide-kinase mediated phosphorylation, which may be slow in many cases. In cases where the nucleoside monophosphate is not a substrate for host nucleotide kinases, activation will be poor and anti-viral efficacy low, even if the triphosphate is an excellent RT inhibitor. In such cases, the generation of metabolites 25 such as (10) may lead to a very significant enhancement in antiviral action. Such compounds may be acting directly in their own right or via a rearrangement, decomposition or disproportionation product or via a contaminant. Moreover, the structure of metabolites such as (10) may be further 30 designed to optimise binding to the known structure of RT, and such modified metabolites could be delivered intracellularly using technology herein described, to 35 further enhance the anti-viral effect.

By "a pharmaceutically acceptable derivative" is meant any pharmaceutically acceptable salt, ester or salt of such ester or any other compound which upon administration to a recipient is capable of providing (directly or indirectly) 5 a compound of formula (1) or (10). By "pharmaceutically acceptable metabolite" is meant a metabolite or residue of a compound of formula (1) or (10) which gives rise to a nucleoside-resistance independent or nucleoside 5'-triphosphate independent mode of reverse transcriptase 10 inhibition exhibited by the compounds of formula (1) or (10).

According to a further aspect of the present invention there is provided a compound according to the present invention 15 for use in a method of treatment, preferably in the prophylaxis or treatment of viral infection.

According to a further aspect of the present invention there is provided use of a compound according to the present 20 invention in the manufacture of a medicament for the prophylaxis or treatment of viral infection.

According to a further aspect of the present invention there is provided a method of prophylaxis or treatment of viral 25 infection comprising administration to a patient in need of such treatment an effective dose of a compound according to the present invention.

The viral infection may comprise any viral infection such as 30 HIV and herpes virus, including HSV 1 and HSV 2, CMV, VZV, EBV, HAV, HBV, HCV, HDV, papilloma, rabies and influenza.

Preferably, the viral infection comprises HIV infection, more preferably HIV-I or HIV-II. It is a feature of the 35 present invention that the compounds exhibit good activity against both HIV-I and HIV-II.

According to a further aspect of the present invention there is provided use of a compound of the present invention in

the manufacture of a medicament for use in the inhibition of a reverse transcriptase by a nucleoside-resistance independent or nucleoside 5'-triphosphate independent mode of action.

5

According to a further aspect of the present invention there is provided a pharmaceutical composition comprising a compound of the present invention in combination with a pharmaceutically acceptable excipient.

10

According to a further aspect of the present invention there is provided a method of preparing a pharmaceutical composition comprising the step of continuing a compound of the present invention with a pharmaceutically acceptable excipient.

15

The medicaments employed in the present invention can be administered by oral or parenteral routes, including intravenous, intramuscular, intraperitoneal, subcutaneous, 20 transdermal, airway (aerosol), rectal, vaginal and topical (including buccal and sublingual) administration.

For oral administration, the compounds of the invention will generally be provided in the form of tablets or capsules, as 25 a powder or granules, or as an aqueous solution or suspension.

Tablets for oral use may include the active ingredient mixed with pharmaceutically acceptable excipients such as inert 30 diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavouring agents, colouring agents and preservatives. Suitable inert diluents include sodium and calcium carbonate, sodium and calcium phosphate, and lactose, while corn starch and alginic acid are suitable 35 disintegrating agents. Binding agents may include starch and gelatin, while the lubricating agent, if present, will generally be magnesium stearate, stearic acid or talc. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate, to delay

absorption in the gastrointestinal tract.

Capsules for oral use include hard gelatin capsules in which the active ingredient is mixed with a solid diluent, and 5 soft gelatin capsules wherein the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin or olive oil.

Formulations for rectal administration may be presented as 10 a suppository with a suitable base comprising for example cocoa butter or a salicylate.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams 15 or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

For intramuscular, intraperitoneal, subcutaneous and 20 intravenous use, the compounds of the invention will generally be provided in sterile aqueous solutions or suspensions, buffered to an appropriate pH and isotonicity. Suitable aqueous vehicles include Ringer's solution and isotonic sodium chloride. Aqueous suspensions according to 25 the invention may include suspending agents such as cellulose derivatives, sodium alginate, polyvinyl-pyrrolidone and gum tragacanth, and a wetting agent such as lecithin. Suitable preservatives for aqueous suspensions include ethyl and n-propyl p-hydroxybenzoate.

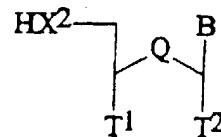
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The compounds of the invention may also be presented as liposome formulations.

In general a suitable dose will be in the range of 0.1 to 35 300 mg per kilogram body weight of the recipient per day, preferably in the range of 6 to 150 mg per kilogram body weight per day and most preferably in the range 15 to 100 mg per kilogram body weight per day. The desired dose is preferably presented as two, three, four, five or six or

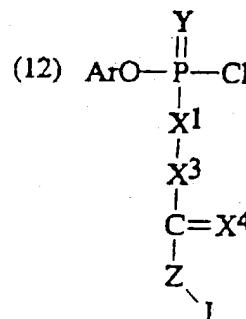
more sub-doses administered at appropriate intervals throughout the day. These sub-doses may be administered in unit dosage forms, for example, containing 10 to 1500 mg, preferably 20 to 1000 mg, and most preferably 50 to 700 mg 5 of active ingredient per unit dosage form.

According to a further aspect of the present invention there is provided a process for the preparation of a compound according to the present invention, the process comprising 10 reaction of a compound of formula (11)



15

with a compound of formula (12)

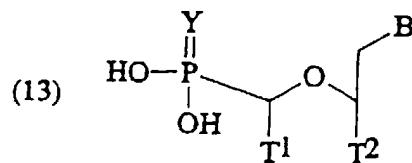


The reaction may be carried out in the tetrahydrofuran in the presence of N-methylimidazole.

30

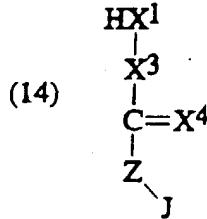
Alternatively, the compounds of the present invention may be prepared by reaction of a compound of formula (13) or a suitable derivative thereof

35



with ArOH and a compound of formula (14) or suitable
5 derivatives thereof

10



15 The invention will now be described with reference to the following Figures and Examples. It will be appreciated that what follows is by way of example only and that modifications to detail may be made whilst still falling within the scope of the invention.

20

Figure 1 illustrates the in vivo antiviral activity of d4T (comparative) and aryl ester phosphoramidate compound 324 in MSV infected mice. Drug doses are 50[low] or 200[high] mg/kg/day given i.p. for 4 days starting 1 hour before MSV
25 inoculation.

EXPERIMENTAL

30

All experiments involving water sensitive compounds were conducted under scrupulously dry conditions. Tetrahydofuran was dried by heating under reflux over sodium and benzophenone followed by distillation and storage over active sieves. N-methylimidazole was purified by distillation. Nucleosides were dried at elevated temperature in vacuo over P₂O₅. Proton, carbon and phosphorus Nuclear Magnetic Resonance (¹H, ¹³C, ³¹P nmr) spectra were recorded on a Bruker Avance DPX spectrometer

operating at 300 MHz, 75.5 MHz, and 121.5 MHz respectively. All nmr spectra were recorded in CDCl₃ at room temperature (20°C +/-3°C). ¹H and ¹³C chemical shifts are quoted in parts per million downfield from tetramethylsilane. ⁵J values refer to coupling constants and signal splitting patterns are described as singlet (s), broad singlet (bs), doublet (d), triplet (t), quartet (q), multiplet (m) or combinations thereof. ³¹P chemical shifts are quoted in parts per million relative to an external phosphoric acid standard. Many NMR peaks were further split due to the presence of diastereoisomers at the [chiral] phosphate centre. Chromatography refers to flash column chromatography and was carried out using Merck silica gel 60H (40-60 m, 230-400 mesh) as stationary phase. Thin layer chromatography was performed using Alugram SIL G/UV₂₅₄ aluminium backed silica gel plates.

Mass spectra were recorded by the fast atom bombardment (FAB) mode on a VG 70--250 spectrometer. HPLC data was recorded using an ACS quaternary system with an ODS5 column and an eluent of water/acetonitrile, with 82% water 0-10 min, and then a linear gradient to 20% water at 30 min, with a flow rate of 2mL/min and detection by UV at 265 nm.

The test compounds were isolated as mixtures of diastereoisomers, with this isomerism arising from mixed stereochemistry at the phosphate centre. The resulting oils did not give useful microanalytical data but were found to be pure by high-field multinuclear NMR spectroscopy and rigorous HPLC analysis.

Preparation of Compounds

The compounds of the present invention were prepared according to the following general procedures.

Preparation of aryl phosphorodichlorides (general procedure)

A solution of the appropriate phenol (30.4 mmol) and

triethylamine (4.25ml, 30.5 mmol) in dry CH_2Cl_2 (25ml) was added to a solution of freshly distilled POCl_3 (10ml, 107mmol) in CH_2Cl_2 (30ml) at -50° and the mixture allowed to stir at ambient temperature overnight. The reaction mixture 5 was filtered and the filtrate evaporated. Ether (20ml) was added and precipitate filtered again. After evaporation the residue was distilled if possible.

Phenyl N-methylalaninyl phosphorochloridate

10 A solution of triethylamine (1ml-7.17mmol) in 15ml of dry CH_2Cl_2 was added dropwise to a mixture of phenyl phosphorodichloridate (757.4mg, 3.59mmol) and L-alanine methyl ester hydrochloride (500mg, 3.58mmol) in 50ml of dry CH_2Cl_2 at -80°C in one hour. The mixture was then stirred 15 vigorously at -50°C during five hours and CH_2Cl_2 evaporated. 25 ml of dry ether was added and precipitate filtered off under nitrogen. Evaporation of ether gave a colourless oil which was used without further purification for the next step.

20

Preparation of aryl phosphates of nucleoside analogues
(general procedure)

Phenyl N-methylalaninyl phosphorochloridate (250 mg, 0.9 mmol, 2.0equivs) was added to a stirred solution of 25 nucleoside analogue 0.45mmol) and N-methyl imidazole (0.37ml, 143.5 μ l, 1.8 mmol, 4equivs) in THF (2ml). After 4 hours, the solvent was removed under reduced pressure. The gum was dissolved in chloroform (10ml), and washed with 1M HCl (8ml), sodium bicarbonate (10ml) and water (15ml). The 30 organic phase was dried, and the solvent removed in vacuo. The residue was purified by column chromatography on silica with elution by chloroform-methanol (97:3). Pooling and evaporation of the eluent gave the product as a white solid.

35 Spectral data

323 - 2',3'-dideoxy-2',3'-didehydrothymidine
5'-(p-ethylphenyl methoxy alaninyl) phosphoramidate

Yield = 79%

³¹P (CDCl₃) : 3.43 ppm

¹H (CDCl₃) : 9.25 (0.5H, s, B, NH), 9.23 (0.5H, s, A, NH), 7.34 (0.5H, s, H-6, B), 7.33 (0.5H, s, H-6, A), 7.14 - 7.00 (5H, m, Ph, H-1'), 6.28 (1H, m, H-3'), 5.88 (1H, m, H-2'), 5.00 (1H, m, H-4'), 4.38 - 4.25 (2H, m, H-5'), 3.93 (2H, m, ala-NH, ala-CH), 3.70 (1.5H, s, OMe, A), 3.67 (1.5H, s, OMe, B), 2.60 (2H, q, CH₂CH₃, J=7.5 Hz), 1.84 (1.5H, d, 5-CH₃, J=1.2 Hz), 1.80 (1.5H, d, 5-CH₃, J=1.2 Hz), 1.31 (3H, m, CH₂CH₃), 1.19 (3H, m, ala-CH₃).

10 ¹³C (CDCl₃) : 174.25 (ala-CO, A), 174.12 (ala-CO, B), 164.22 (C-4, B), 164.17 (C-4, A), 151.15 (C-2, B), 151.12 (C-2, A), 148.29 (i-Ph, B), 148.16 (i-Ph, A), 141.24 (p-Ph, A), 141.19 (p-Ph, B), 136.06 (C-6, B), 135.76 (C-6, A), 133.50 (C-3', A), 133.15 (C-3', B), 129.11 (o-Ph, A), 129.05 (o-Ph, B), 15 127.54 (C-2', A), 127.36 (C-2', B), 120.08 (d, m-Ph, B, J=3.9 Hz), 119.90 (d, m-Ph, A, J=4.9 Hz), 111.51 (C-5, A), 111.40 (C-5, B), 89.83 (C-1', B), 89.60 (C-1', A), 84.88 (d, C-4', B, J=8.8 Hz), 84.70 (d, C-4', A, J=8.8 Hz), 67.11 (d, C-5', A, J=4.9 Hz), 66.48 (d, C-5', B, J=4.9 Hz), 52.65 20 (OMe), 50.26 (ala-CH, B), 50.13 (ala-CH, A), 28.19 (Ph-CH₂), 20.97 (d, ala-CH₃, B, J=4.9 Hz), 20.90 (d, ala-CH₃, A, J=4.9 Hz), 15.69 (Ph-CH₂CH₃), 12.45 (5-CH₃, A), 12.41 (5-CH₃, B).

MS : C₂₂H₂₉N₃O₈P : 494 (MH⁺, 5), 368 (MH⁺-thymine, 25), 228 (15), 81 (C₅H₅O, base peak) Accurate mass : expected 25 494.1692; found 494.1693

HPLC : RT = 27.23 and 27.48 min

324 - 2',3'-dideoxy-2',3'-didehydrothymidine 5'-(phenyl 30 N-methoxy alaninyl) phosphoramidate

Yield = 88%

³¹P (CDCl₃) : 3.20 and 3.86 ppm

¹H (CDCl₃) : 1.32 and 1.34 (d, 3H, J=6.8Hz, CH, ala); 1.81 and 1.84 (d, 3H, 5CH₃); 3.69 and 3.70 (s, 3H, OMe); 35 3.84-4.00 (m, 2H, CH ala + NH ala); 4.32 (m, 2H, H5'); 5.02 (m, 1H, H4'); 5.88 (m, 1H, H2'); 6.33 (m, 1H, H3'); 7.03 (m, 1H, H1'); 7.15-7.35 (m, 6H, Ar + H6); 9.22 and 9.26 (bs, 1H, NH)

¹³C (CDCl₃) : 12.52 (5CH₃); 21.02 (CH₃, ala); 50.22-50.35 (CH

ala); 52.74 (OMe); 66.62-67.29 (C5'); 84.80-84.88 (C4'); 89.69-89.93 (C1'); 111.44-111.57 (C5); 120.13-120.31 (Ar ortho); 125.30 (Ar para); 127.49-127.65 (C2'); 129.87-129.93 (Ar meta); 133.19-133.50 (C3'); 135.77-136.06 (C6); 150.51 (Ar ipso); 151.16 (C2); 164.14 (C4); 174.12 (CO ala)
 5 MS : 466 (MH⁺, 7); 340 (MH⁺-base); 200 (17); 136 (47); 89 (25); 81 (C₅H₅O, base peak)
 HPLC : RT = 22.48 and 22.87 min

10 327 - 2',3'-dideoxy-2',3'-didehydrothymidine
5'-(p-fluorophenyl methoxy alaninyl) phosphoramidate

Yield = 89%

³¹P (CDCl₃) : 3.16 ppm

¹H (CDCl₃) : 9.75 (1H, s, NH), 7.24 (0.5H, d, H-6, B, J=1.2 Hz), 7.17 (0.5H, d, H-6, A, J=1.2 Hz), 7.09 (5H, m, Ph, H-1'), 6.22 (1H, m, H-3'), 5.82 (1H, m, H-2'), 4.94 (1H, m, H-4'), 4.30-3.84 (4H, m, ala-NH, ala-CH, H-5'), 3.63 (1.5H, s, OMe, A), 3.62 (1.5H, s, OMe, B), 1.77 (1.5H, d, 5-CH₃, B, J=1.0 Hz), 1.74 (1.5H, d, 5-CH₃, A, J=1.0 Hz), 1.29 (1.5H, 20 d, ala-CH₃, B, J=7.0 Hz), 1.23 (1.5H, d, ala-CH₃, A, J=7.0 Hz).

¹³C (CDCl₃) : 174.19 (d, ala-CO, B, J=6.8 Hz), 174.00 (d, ala-CO, A, J=6.8 Hz), 164.25 (C-4, B), 164.20 (C-4, A), 159.77 (d, p-Ph, J=243.6 Hz), 151.14 (C-2), 146.25 (i-Ph), 25 135.99 (C-6, A), 135.70 (C-6, B), 133.40 (C-3', A), 133.05 (C-3', B), 127.61 (C-2', B), 127.45 (C-2', A), 121.70 (m, o-Ph), 116.37 (d, m-Ph, A, J=23.5 Hz), 116.34 (d, m-Ph, B, J=23.5 Hz), 111.45 (C-5, A), 111.32 (C-5, B), 89.87 (C-1', A), 89.63 (C-1', B), 84.66 (d, C-4', J=5.9 Hz), 67.29 (d, 30 C-5', A, J=4.9 Hz), 66.10 (d, C-5', B, J=4.9 Hz), 52.70 (OMe), 50.26 (ala-CH, A), 50.13 (ala-CH, B), 20.92 (d, ala-CH₃, A, J=4.8 Hz), 20.88 (d, ala-CH₃, B, J=4.8 Hz), 12.45 (5-CH₃, B), 12.41 (5-CH₃, A).

MS : C₂₀H₂₄N₃O₈PF : 484 (MH⁺, 11), 358 (MH⁺-thymine, 20), 218 (13), 154 (32), 136 (28), 81 (C₅H₅O, base peak). Accurate mass : expected 484.1285; found 484.1318

HPLC : RT = 25.17 and 25.40 min

526 - 2',3'-dideoxy-2',3'-didehydrothymidine

5'-(m-trifluoromethylphenyl methoxy alaninyl) phosphoramidate

Yield = 80%

³¹P (CDCl₃) : 2.49 and 3.16 ppm¹H (CDCl₃) : 9.06 (1H, s, NH), 7.45 (5H, m, H-6, Ph), 7.03

5 (1H, m, H-1'), 6.31 (1H, m, H-3'), 5.92 (1H, m, H-2'), 5.03 (1H, m, H-4'), 4.32 (2H, m, H-5'), 3.97 (2H, m, ala-NH, ala-CH), 3.71 (1.5H, s, OMe, B), 3.70 (1.5H, s, OMe, A), 1.86 (1.5H, s, 5-CH₃, B), 1.80 (1.5H, d, 5-CH₃, A), 1.36 (3H, m, ala-CH₃).

10 ¹³C (CDCl₃) : 174.06 (d, ala-CO, A, J=6.8 Hz), 173.89 (d, ala-CO, B, J=6.8 Hz), 163.91 (C-4, A), 163.86 (C-4, B), 150.96 (C-2), 150.71 (d, a-Ph, J=5.9 Hz), 135.86 (C-6, A), 135.66 (C-6, B), 133.30 (C-3', A), 133.02 (C-3', B), 132.00 (q, c-Ph, J=32.0 Hz), 130.66 (e-Ph), 127.84 (C-2', B),

15 127.74 (C-2', A), 123.98 (f-Ph, A), 123.84 (q, CF₃, J=272.0 Hz), 123.79 (f-Ph, B), 122.14 (d-Ph), 117.54 (d, b-Ph, J=3.9 Hz), 111.61 (C-5, B), 111.44 (C-5, A), 90.04 (C-1', B), 89.77 (C-1', A), 84.61 (d, C-4', J=7.8 Hz), 67.60 (d, C-5', B, J=4.9 Hz), 66.89 (d, C-5', A, J=4.9 Hz), 52.87 (OMe),

20 50.32 (d, ala-CH, A, J=4.8 Hz), 50.26 (d, ala-CH, B, J=4.8 Hz), 21.11 (d, ala-CH₃, B, J=4.9 Hz), 20.99 (d, ala-CH₃, A, J=4.9 Hz), 12.55 (5-CH₃, B), 12.47 (5-CH₃, A).

MS : C₂₁H₂₄N₃O₈PF₃ : 534 (MH⁺, 6), 408 (MH⁺-thymine, 8), 268 (10), 149 (10), 81 (C₅H₅O, base peak). Accurate mass :

25 expected 534.1253; found 534.1201

HPLC : RT = 30.56 min

546 - 2',3'-dideoxy-2',3'-didehydrothymidine30 5'-(3,5-dichlorophenyl methoxy alaninyl) phosphoramidate

Yield = 70%

³¹P (CDCl₃) : 2.83 and 3.42 ppm¹H (CDCl₃) : 9.74 (1H, s, NH), 7.40 (1H, s, H-6), 7.29 (3H, m, Ph), 7.14 (1H, m, H-1'), 6.44 (1H, m, H-3'), 6.04 (1H, m,

35 H-2'), 5.14 (1H, m, H-4'), 4.48 - 4.07 (5H, m, ala-NH, ala-CH, H-5'), 3.84 (3H, s, OMe), 1.97 (1.5H, s, 5-CH₃, A), 1.92 (1.5H, s, 5-CH₃, B), 1.48 (3H, m, ala-CH₃).

¹³C (CDCl₃) : 173.93 (ala-CO), 164.09 (C-4), 151.27 (i-Ph), 151.06 (C-2), 136.01 (m-Ph), 135.60 (C-6), 133.14 (C-3', B),

132.89 (C-3', A), 127.83 (C-2'), 125.69 (p-Ph), 119.40 (o-Ph), 111.54 (C-5, A), 111.40 (C-5, B), 90.03 (C-1', A), 89.74 (C-1', B), 84.60 (C-4'), 67.68 (C-5', A), 66.98 (C-5', B), 52.85 (OMe), 50.26 (ala-CH), 20.93 (ala-CH₃),

5 12.51 (5-CH₃).

MS : C₂₀H₂₃N₃O₈PCl₂ : 534 (MH⁺, 8), 408 (MH⁺-thymine, 12), 391 (10), 149 (12), 127 (thymineH⁺, 12), 81 (C₃H₅O, base peak).

Accurate mass : expected 534.0600; found 534.0589

HPLC : RT = 32.19 min

10

730 - 2',3'-dideoxy-2',3'-didehydrothymidine-5'-(phenyl N-benzylxy alaninyl) phosphoramidate

Yield = 92%

³¹P (CDCl₃) : 3.40 and 4.04 ppm

15 ¹H (CDCl₃) : 1.24 and 1.26 (d, 3H, J=6.8Hz, CH, ala); 1.70 and 1.74 (s, 3H, 5CH₃); 3.86-4.28 (m, 4H, H5'+CH ala+NH); 4.85 (m, 1H, H4'); 5.04 and 5.06 (s, 2H, CH₂Ph); 5.74 (d, 1H, H2'); 6.16 (dd, 1H, H3'); 6.90 (m, 1H, H1'); 7.00-7.30 (m, 11H, Ar + H6); 9.61 (d, 1H, NH)

20 ¹³C (CDCl₃) : 12.52 (5CH₃); 20.98 (CH₃, ala); 50.36-50.52 (CH ala); 66.70-67.18 (C5'); 67.46 (CH₂Ph); 84.63-84.76-84.88 (C4'); 89.68-89.88 (C1'); 111.44-111.55 (C5); 120.18-120.25-120.36-120.43 (Ar ortho, OPh); 125.31 (Ar para, OPh); 127.48-127.61 (C2'); 128.45-128.79-128.83 (Ar, CH₂Ph); 129.87-129.93 (Ar meta, OPh); 133.16-133.45 (C3'); 135.35 (Ar1, CH₂Ph); 135.79-136.07 (C6); 150.44 (Ar1, OPh); 151.18 (C2); 164.21-164.28 (C4); 173.42-173.51-173.65 (CO ala)

HPLC : RT = 34.96 and 35.07 min

30 MS : C₂₆H₂₆O₈N₃P : 542 (MH⁺; 17); 416 (MH⁺base; 40); 81 (100).

Accurate mass : expected 542.1716; found 542.1712

776 - 2',3'-dideoxy-2',3'-didehydrothymidine-5'-(2,4-dibromophenyl N-methylalaninyl) phosphoramidate

35 Yield = 88%

³¹P (CDCl₃) : 3.07 and 3.62 ppm

¹H (CDCl₃) : 1.26 and 1.28 (d, 3H, J=6.8Hz, CH, ala); 1.75 and 1.80 (s, 3H, 5CH₃); 2.11 (s, 1H, NH); 3.64 (s, 3H, OMe); 3.92-4.30 (m, 3H, H5'+CHala); 4.98 (m, 1H, H4'); 5.87 (m,

1H, H2'); 6.26 (m, 1H, H3'); 6.96 (m, 1H, H1'); 7.30-7.60 (m, 4H, Ar + H6); 9.41 (bs, 1H, NH)

¹³C (CDCl₃) : 12.51 (5CH₃); 21.00 (CH₃ ala); 50.24 (CHala); 52.80 (OMe); 67.37-67.83 (C5'); 84.49-84.61 (C4');

5 89.80-89.92 (C1'); 111.60 (C5); 115.49 (Ar2); 118.26 (Ar4); 122.61-122.89 (Ar6); 127.70 (C2'); 131.86 (Ar5); 133.06-133.21 (C3'); 135.64 (Ar3); 135.75-135.88 (C6); 147.01 (Ar1); 151.07 (C2); 164.03 (C4); 173.71-173.82 (COala)

10 HPLC : RT = 41.17 and 41.30 min

MS : C₂₀H₂₂O₈N₃PBr₂ : 622, 624, 626 (MH⁺; 3, 6, 3); 496, 498, 500 (MH⁺base; 5, 9, 5); 81 (100). Accurate mass : expected 621.9516; found 621.9507

15 779 - 2',3'-dideoxy-2',3'-didehydrothymidine-5'-(2,3,4,5,6-pentafluorophenyl-N-methylalaninyl)phosphoramidate

Yield = 76%

³¹P (CDCl₃) : 4.74 and 5.66 ppm

¹H (CDCl₃) : 1.34 and 1.36 (d, 3H, J=6.7Hz, CH₃ ala); 1.75 and 1.81 (s, 3H, 5CH₃); 3.69 (s, 3H, OMe); 3.92-4.40 (m, 4H, H5'+CH ala+NH); 4.97 (m, 1H, H4'); 5.85 (m, 1H, H2'); 6.29 (m, 1H, H3'); 6.93 (m, 1H, H1'); 7.19 (m, 1H, H6); 9.38 (bs, 1H, NH)

¹³C (CDCl₃) : 12.23-12.43 (5CH₃); 20.83 (CH₃ ala); 50.22-50.34 (CH ala); 52.99 (OMe); 67.75-68.37 (C5'); 84.42-84.52 (C4'); 89.87-90.17 (C1'); 111.75 (C5); 127.69-127.93 (C2'); 132.86-133.13 (C3'); 132-143 (m, Ar); 135.74-135.96 (C6); 151.11 (C2); 164.15 (C4); 173.64-173.76 (COala)

30 Mass (NOBA matrix) : C₂₀H₁₉O₈N₃PF₅ : 556 (MH⁺, 31); 578 (M⁺Na, 100)

HPLC : RT = 35.90 min

862 - 2',3'-dideoxy-2',3'-didehydrothymidine 5'-(phenyl

35 N-hexyloxy alaninyl)phosphoramidate

Yield = 88%

³¹P (CDCl₃) : 3.99 and 4.60 ppm

¹H (CDCl₃) : 0.94 (m, 3H, CH₃CH₂); 1.28-1.41 (m, 9H, CH₃ ala + 3xCH₂); 1.65 (m, 2H, CO₂CH₂CH₂); 1.90 and 1.93 (s, 3H,

5CH₃); 4.00-4.20 (m, 4H, CH ala + NH ala + CO₂CH₂); 4.37 (m, 2H, H5'); 5.05 (m, 1H, H4'); 5.94 (m, 1H, H2'); 6.38 (m, 1H, H3'); 7.10 (m, 1H, H1'); 7.15-7.36 (m, 6H, Ar + H6); 9.48 and 9.51 (s, 1H, NH)

5 ¹³C (CDCl₃) : 12.76 (5CH₃); 14.39 (CH₂CH₂); 21.45 (CH₃ ala); 22.88, 25.82, 28.82 and 31.72 (CH₂); 50.63 (CH ala); 66.26 (OCH₂); 66.89-67.43 (C5'); 85.03 (C4'); 89.97 (C1'); 111.68-111.83 (C5); 120.55 (Ar ortho); 125.57 (Ar para); 127.86 (C2'); 130.15 (Ar meta); 133.47-133.70 (C3');

10 136.03-136.31 (C6); 150.72 (Ar ipso); 151.37-151.39 (C2); 164.35-164.42 (C4); 174.02 (CO ala)

Mass (NOBA matrix) : C₂₃H₃₄O₈N₃P : 536 (MH⁺, 24); 558 (M⁺Na, 37)

15 863 - 2',3'-dideoxy-2',3'-didehydrothymidine-5'-(phenyl N-methoxy-phenylalaninyl) phosphoramidate

Yield = 89%

³¹P (CDCl₃) : 3.96 and 4.35 ppm

1 ¹H (CDCl₃) : 1.89 (s, 3H, 5CH₃); 3.00 (m, 2H, CH₂Ph); 3.74 (s, 3H, OMe); 3.80-4.28 (m, 4H, CH ala + NH ala + H5'); 4.94 (m, 1H, H4'); 5.91 (m, 1H, H2'); 6.21-6.30 (m, 1H, H3'); 7.04-7.32 (m, 12H, Ar + H1' + H6); 9.35 (s, 1H, NH)

5 ¹³C (CDCl₃) : 12.54 (5CH₃); 40.55 (CH₂Ph); 52.63 (OMe); 55.72-56.01 (CH ala); 66.50-67.10 (C5'); 84.78 (C4');

20 89.71-89.95 (C1'); 111.53-111.64 (C5); 120.28 (Ar ortho, OPh); 125.40 (Ar para, OPh); 127.52 (C2'); 128.86, 129.65 and 129.98 (Ar, CH₂Ph); 129.86-129.92 (Ar meta, OPh); 133.18-133.50 (C3'); 135.72 (Ar ipso, CH₂Ph); 135.79-136.06 (C6); 150.46 (Ar ipso, OPh); 151.13-151.17 (C2); 30 164.12-164.18 (C4); 173.00 (CO ala)

Mass (NOBA matrix) : C₂₆H₂₈O₈N₃P : 542 (MH⁺, 77); 564 (M⁺Na, 29)

864 - 2',3'-dideoxy-2',3'-didehydrothymidine-5'-(phenyl N-methoxy-leucinyl) phosphoramidate

Yield = 87%

³¹P (CDCl₃) : 4.18 and 4.83 ppm

1 ¹H (CDCl₃) : 0.91 (m, 6H, (CH₃)₂CH); 1.42-1.70 (m, 3H, CH₂CH(CH₃)₂); 1.91 and 1.93 (s, 3H, 5CH₃); 3.73 (s, 3H, OMe);

3.76-3.98 (m, 2H, CH ala + NH ala); 4.28-4.46 (m, 2H, H5'); 5.08 (m, 1H, H4'); 5.96 (m, 1H, H2'); 6.36 (m, 1H, H3'); 7.09 (m, 1H, H1'); 7.18-7.35 (m, 6H, Ar + H6); 9.35 (s, 1H, NH)

5 ^{13}C (CDCl₃) : 12.76 (5CH₃); 22.23-23.01 ((CH₃)₂CH); 24.75 (CH(CH₃)₂); 43.86-44.11 (CH₂CH(CH₃)₂); 52.75 (OMe); 53.42-53.60 (CH ala); 66.92-67.55 (C5'); 85.62 (C4'); 89.92-90.19 (C1'); 111.69-111.83 (C5); 120.37-120.62 (Ar ortho); 125.55-125.58 (Ar para); 127.79 (C2'); 130.12 (Ar meta); 133.51-133.70 (C3'); 136.00-136.36 (C6); 151.05 (Ar ipso); 151.38 (C2); 164.39-164.50 (C4); 174.55-174.88 (CO ala)

Mass (NOBA matrix) : C₂₃H₃₀O₈N₃P : 508 (MH⁺, 62); 530 (M⁺Na, 59)

15

865 - 2',3'-dideoxy-2',3'-didehydrothymidine-5'-(phenyl N-methoxyvalinyl) phosphoramidate

Yield = 86%

^{31}P (CDCl₃) : 4.85 and 5.40 ppm

20 ^1H (CDCl₃) : 0.92 (m, 6H, (CH₃)₂CH); 1.82 (m, 3H, CH(CH₃)₂); 1.89 and 1.91 (s, 3H, 5CH₃); 3.76 (s, 3H, OMe); 3.82 (m, 2H, CH ala + NH ala); 4.30-4.48 (m, 2H, H5'); 5.07 (m, 1H, H4'); 5.96 (m, 1H, H2'); 6.38 (m, 1H, H3'); 7.10 (m, 1H, H1'); 7.18-7.35 (m, 6H, Ar + H6); 9.31 (s, 1H, NH)

25 ^{13}C (CDCl₃) : 12.80 (5CH₃); 17.77-19.24 ((CH₃)₂CH); 32.43-32.62 (CH(CH₃)₂); 52.67 (OMe); 60.32-60.38 (CH ala); 66.92-67.65 (C5'); 85.04 (C4'); 89.98-90.24 (C1'); 111.76-111.87 (C5); 120.45-120.56 (Ar ortho); 125.54-125.59 (Ar para); 127.81-127.86 (C2'); 130.13-130.17 (Ar meta); 133.51-133.72 (C3'); 136.01-136.28 (C6); 150.83 (Ar ipso); 150.87-151.34 (C2); 164.30-164.37 (C4); 173.56-173.65 (CO ala)

Mass : C₂₂H₂₈O₈N₃P : 493.6 (MH⁺, 100)

866 - 2',3'-dideoxy-2',3'-didehydrothymidine-5'-(phenyl

N-methoxyglycinyl) phosphoramidate

Yield = 90%

^{31}P (CDCl₃) : 4.89 and 5.52 ppm

^1H (CDCl₃) : 1.79 and 1.83 (s, 3H, 5CH₃); 3.69 (s, 3H, OMe); 3.70-4.05 (m, 4H, CH₂NH + CH ala + NH ala); 4.32 (m, 2H,

H5'); 4.99 (m, 1H, H4'); 5.92 (m, 1H, H2'); 6.38 (m, 1H, H3'); 6.98 (m, 1H, H1'); 7.05-7.38 (m, 6H, Ar + H6); 9.44 and 9.46 (s, 1H, NH)

¹³C (CDCl₃) : 12.75 (5CH₃); 43.15 (CH₂NH); 52.94 (OMe); 66.78
 5 -67.52 (C5'); 84.98-85.10 (C4'); 89.68-90.16 (C1'); 111.69-111.80 (C5); 120.46-120.59 (Ar ortho); 125.66 (Ar para); 127.66-127.91 (C2'); 130.22 (Ar meta); 133.48-133.87 (C3'); 136.11-136.40 (C6); 150.65 (Ar ipso); 151.45 (C2); 164.46 (C4); 171.41-171.51 (CO ala)
 10 Mass (NOBA matrix) : C₁₉H₂₂O₈N₃P : 452 (MH⁺, 74); 474 (M⁺Na, 46)

867 - 2',3'-dideoxy-2',3'-didehydrothymidine-5'-(phenyl N-methoxymethioninyl) phosphoramidate

15 Yield = 81%

³¹P (CDCl₃) : 4.09 and 4.86 ppm
¹H (CDCl₃) : 1.74 and 1.79 (s, 3H, CH₃S); 1.94 and 1.97 (s, 3H, 5CH₃); 1.80-2.40 (m, 5H, CH₂CH₂CH₂S); 3.72 and 3.74 (s, 3H, OMe); 3.98-4.32 (m, 4H, H5' + CH ala + NH ala); 4.96 (m, 1H, H4'); 5.84 (m, 1H, H2'); 6.26 (m, 1H, H3'); 6.96 (m, 1H, H1'); 7.05-7.25 (m, 6H, Ar + H6); 9.58 (bs, 1H, NH)
¹³C (CDCl₃) : 12.80 (5CH₃); 15.68 (CH₃S); 29.95 (CH₂SCH₃); 33.73-33.85 (CH₂CH₂S); 53.06 (OMe); 53.81-54.07 (NHCH); 67.05-67.70 (C5'); 84.90-85.03 (C4'); 89.98-90.23 (C1'); 111.66-111.86 (C5); 120.39-120.66 (Ar ortho); 125.63 (Ar para); 127.81-127.91 (C2'); 130.18 (Ar meta); 133.44-133.69 (C3'); 136.00-136.38 (C6); 150.72-150.80 (Ar ipso); 151.41 (C2); 164.52 (C4); 173.61-173.94 (CO ala)

30 Mass (NOBA matrix) : C₂₂H₂₈O₈N₃PS : 526 (MH⁺, 46); 548 (M⁺Na, 21)

868 - 2',3'-dideoxy-2',3'-didehydrothymidine-5'-(2,4-dibromophenyl N-benzylalaninyl) phosphoramidate

35 Yield = 82%

³¹P (CDCl₃) : 3.68 and 4.18 ppm
¹H (CDCl₃) : 1.40 and 1.42 (d, 3H, J=6.7Hz, CH₃ ala); 1.90 and 1.92 (s, 3H, 5CH₃); 4.04-4.40 (m, 4H, H5'+CHala + NH ala); 4.98 (m, 1H, H4'); 5.20 (s, 2H, CH₂Ph); 5.91 (m, 1H,

H2'); 6.27 and 6.35 (m, 1H, H3'); 7.06 (bs, 1H, H1'); 7.30-7.70 (m, 9H, Ar + H6); 9.52 (s, 1H, NH)

¹³C (CDCl₃) : 12.86 (5CH₃); 21.35 (CH₃, ala); 50.68-50.76 (CHala); 67.67-68.03 (C5'); 67.88 (CH₂Ph); 84.85 (C4');

5 90.10-90.20 (C1'); 111.88-111.92 (C5); 115.76-115.91 (Ar2); 118.62-118.72 (Ar4); 122.91-123.22 (Ar6); 127.98 (C2'); 128.75-129.01-129.12 (Ar o,m,p, CH₂Ph); 132.20 (Ar5); 133.38-133.51 (C3'); 135.48 (Ar ipso, CH₂Ph); 135.96 (Ar3); 136.21 (C6); 147.28 (Ar1); 151.39 (C2); 164.34-164.38 (C4); 10 173.47-173.62 (COala)

Mass (NOBA matrix) : C₂₆H₂₆O₈N₃PBr₂ : 699-700-701 (MH⁺+, 27-49-29); 721-722-723 (M⁺Na, 17-21-17)

877 - 2',3'-dideoxy-2',3'-didehydrothymidine-5'-(phenyl N-methoxyglycinyl) phosphoramidate

Yield = 83%

³¹P (CDCl₃) : 3.91 and 4.33 ppm

¹H (CDCl₃) : 1.83 and 1.85 (s, 3H, 5CH₃); 3.01 (m, 2H, CHCH₂Ph); 3.78-4.30 (m, 4H, H5' + HNCH); 4.92 (m, 1H, H4'); 20 5.89 (m, 1H, H2'); 6.18 and 6.27 (m, 1H, H3'); 7.00-7.40 (m, 17H, Ar + H1' + H6); 9.35 (bs, 1H, NH)

¹³C (CDCl₃) : 12.62-12.75 (5CH₃); 40.65-40.73 (CH₂Ph); 55.95-56.26 (NHCH); 66.79 -67.27 (C5'); 67.80 (CH₂Ph); 84.87-85.05 (C4'); 89.92-90.14 (C1'); 111.72-111.82 (C5); 25 120.45-120.52 (Ar ortho, OPh); 125.60 (Ar para, OPh); 127.73 (C2'); 129.01- 129.07-129.11-129.91- 130.15-130.38- 135.29-135.85 (Ar, 2xCH₂Ph); 130.21 (Ar meta, OPh); 133.36-133.63 (C3'); 136.24 (C6); 150.68-150.77 (Ar ipso, OPh); 151.31-151.35 (C2); 164.28-164.34 (C4); 172.48-172.64 30 (CO ala)

Mass (NOBA matrix) : C₃₂H₃₂O₈N₃P : 618 (MH⁺+, 78); 640 (M⁺Na, 52)

878 - 2',3'-dideoxy-2',3'-didehydrothymidine-5'-(phenyl N-tert-butylphenylalaninyl) phosphoramidate

Yield = 79%

³¹P (CDCl₃) : 4.27 and 4.50 ppm

¹H (CDCl₃) : 1.40 and 1.41 (s, 9H, tBu); 1.84 and 1.87 (s, 3H, 5CH₃); 3.00 (m, 2H, CH₂Ph); 3.76-4.28 (m, 4H, H5' +

HNCH); 4.95 (m, 1H, H4'); 5.86 and 5.91 (m, 1H, H2'); 6.26 and 6.30 (m, 1H, H3'); 7.04 (m, 1H, H1'); 7.12-7.25 (m, 11H, Ar + H6); 9.38 and 9.40 (bs, 1H, NH)

^{13}C (CDCl₃) : 12.76-12.79 (5CH₃); 28.31 ((CH₃)₂C); 40.96-41.04 5 (CH₂Ph); 56.31-56.65 (NHCH); 66.79-67.28 (C5'); 82.90-82.92 ((CH₃)₂C); 84.94-85.03 (C4'); 89.93-90.11 (C1'); 111.67-111.86 (C5); 120.45 (Ar ortho, OPh); 125.52 (Ar para, OPh); 127.77 (C2'); 127.88-128.83-128.92-136.02 (Ar, CH₂Ph); 130.13 (Ar meta, OPh); 133.54-133.60 (C3'); 136.31 (C6); 10 150.75-150.84 (Ar ipso, OPh); 151.36 (C2); 164.32-164.37 (C4); 171.89 (CO ala)

Mass (NOBA matrix) : C₂₉H₃₄O₈N₃P : 584 (MH⁺, 26); 606 (M⁺Na, 41)

15 892 - 2',3'-dideoxy-2',3'-didehydrothymidine 5'-(phenyl N-cyclohexyloxy alaninyl) phosphoramidate

Yield = 83%

^{31}P (CDCl₃) : 4.11 and 4.71 ppm.

^1H (CDCl₃) : 1.08-1.82 (m, 16H, CH, ala + 5CH₃ + cyclohexyl); 20 3.79-4.14 (m, 2H, CH ala + NH ala); 4.27 (m, 2H, H5'); 4.69 (m, CH cyclohexyl); 4.96 (m, 1H, H4'); 5.80 (m, 1H, H2'); 6.24 (m, 1H, H3'); 6.98 (m, 1H, H1'); 7.04-7.32 (m, 6H, Ar + H6); 9.66 and 9.82 (bs, 1H, NH).

^{13}C (CDCl₃) : 12.58 (5CH₃); 21.18-21.32 (CH, ala); 25 23.73-25.40-31.49-31.58 (CH, cyclohexyl); 50.47-50.61 (CH ala); 66.69-67.24 (C5'); 74.36 (CH cyclohexyl); 84.87 (C4'); 89.72-89.92 (C1'); 111.48-111.63 (C5); 120.26-120.49 (Ar ortho); 125.32-125.37 (Ar para); 127.59-127.73 (C2'); 129.91-129.98 (Ar meta); 133.30-133.51 (C3'); 135.89-136.16 30 (C6); 150.53 (Ar ipso); 150.67-151.31 (C2); 164.36-164.41 (C4); 173.23 (CO ala).

Mass (NOBA matrix) : C₂₅H₃₂O₈N₃P : 534 (MH⁺, 56); 556 (M⁺Na, 42)

35 893 - 2',3'-dideoxy-2',3'-didehydrothymidine 5'-(phenyl N-tButyloxy alaninyl) phosphoramidate

Yield = 79%

^{31}P (CDCl₃) : 4.17 and 4.67 ppm.

^1H (CDCl₃) : 1.34 (m, 3H, CH, ala); 1.46 (m, 9H, CH, tBu);

1.87 (d, 3H, 5CH₃); 3.82-4.06 (m, 2H, H5'); 4.29-4.49 (m, 2H, CH ala + NH ala); 5.05 (m, 1H, H4'); 5.91 (m, 1H, H2'); 6.35 (m, 1H, H3'); 7.06 (m, 1H, H1'); 7.15-7.40 (m, 6H, Ar +H6); 9.60 (bs, 1H, NH).

5 ¹³C (CDCl₃) : 12.54 (5CH₃); 21.19-21.35 (CH₂ ala); 28.07 (C(CH₃)₃); 50.80-50.89 (CH ala); 66.60-67.18 (C5'); 82.41-82.45 (C(Me)₃); 84.82 (C4'); 89.67-89.87 (C1'); 111.44-111.60 (C5); 120.22-120.41 (Ar ortho); 125.28-125.31 (Ar para); 127.54-127.65 (C2'); 129.88-129.94 (Ar meta); 10 133.33-133.47 (C3'); 135.84-136.10 (C6); 150.51 (Ar ipso); 150.65-151.20 (C4); 164.19 -164.23 (C2); 172.78-172.93 (CO ala).

Mass (NOBA matrix) : C₂₃H₃₀O₈N₃P : 508 (MH⁺, 82); 530 (M⁺⁺Na, 48).

15 2', 3'-Dideoxy-2', 3'-dihydrothymidine-5'- (phenyl methoxy-B-alaninyl) phosphate

Cf 1197

Yield=64%

³¹P (CDCl₃) : 6.44, 6.70 (1:3)

20 1H (CDCl₃) : 1.87^{*} (s, 3H, 5-CH₃), 2.42(t, 2H, CH₂ ala), 3.22^{*} (m, 2H, CH₂ ala), 3.62 (s, 3H, OCH₃), 4.09 (m, 1H, H4'), 4.18-4.39 (m, 2H, H5'), 4.97 (bs, 1H, NH ala), 5.88^{*} (m, 1H, H2'), 6.32^{*} (m, 1H, H3'), 6.99 (m, 1H, H1'), 7.08-7.38 (m, 5H, Ph and H6), 10.01 (bs, 1H, base NH)

25 ¹³C (CDCl₃) : 14.52 (5-CH₃), 37.80^{*} (CH₂ ala), 39.28^{*} (CH₂ ala), 53.91^{*} (OCH₃), 68.57^{*} (d, J = 3.92 Hz, C5'), 86.90 (d, J = 8.38 Hz, C4'), 91.68^{*} (C1'), 113.40^{*} (C5), 122.34 (d, J = 4.68 Hz, ortho-Ph), 127.23 (C2'), 129.55^{*} (para-Ph), 131.81^{*} (meta-Ph), 135.45^{*} (C6), 137.99^{*} (C3'), 152.60^{*} (d, J = 5.96 Hz, ipso-Ph), 153.44 (C2), 166.58 (C4), 174.55^{*} (COO)

Mass (NOBA matrix) : C₂₀H₂₄N₃O₈P 126 (thymine⁺, 5), 127 (thymineH⁺, 4), 242 (C₁₀H₁₃PO₄N⁺, 9), 243 (C₁₀H₁₄PO₄N⁺, 3), 465 (M⁺, 4), 466 (MH⁺, 8), 467 (MHNa⁺, 20), 168 (MHNa⁺, ¹³O, 5), 187 (MNa⁺, 3), 188 (MHNa⁺, 97), 189 (MHNa⁺, ¹³C, 21)

35 High Resolution MS: found 466.1379 (MH⁺), C₂₀H₂₅N₃O₈P requires 466.1379

HPLC: RT = 22.81, 23.27 mins (1:1)

2', 3'-Dideoxy-2', 3'-didehydrothymidine-5'-(phenyl methoxy-
α-aminobutylrlyl) phosphate

Cf 1198

Yield = 65%

5 ^{31}P (CDCl_3): 6.11, 6.66 (1:2)
 ^1H (CDCl_3): 1.78 (m, 2H, CH_2 GABA), 1.85° (s, 3H, 5- CH_3), 2.35 (t, 2H, J = 6.95 Hz, CH_2 GABA), 2.97° (m, 2H, CH_2 GABA), 3.68 (s, 3H, OCH_3), 3.93° (m, 1H, $\text{H}4'$), 4.28° (m, 1H, $\text{H}5'$), 4.35° (m, 1H, $\text{H}5'$), 5.02 (bs, 1H, NH GABA), 5.82° (m, 1H, $\text{H}2'$),
10 6.31 (m, 1H, $\text{H}3'$), 6.98 (m, 1H, $\text{H}1'$), 7.11-7.37 (m, 6H, Ph and $\text{H}6$), 9.91 (bs, 1H, base NH)
 ^{13}C (CDCl_3): 12.64 (5- CH_3), 26.72° (CH_2 GABA), 32.25° (CH_2 GABA), 40.98° (CH_2 GABA), 51.94 (OCH_3), 66.93° ($\text{C}5'$), 85.11 (d, J = 8.30 Hz, $\text{C}4'$), 111.40 ($\text{C}5$), 120.46° (d, J = 4.83 Hz, ortho-
15 PH), 125.24 ($\text{C}2'$), 127.59° (para-Ph), 129.88° (meta-Ph), 133.68° ($\text{C}6$), 136.28° ($\text{C}3'$), 150.86° (d, J = 6.45 Hz, ipso-
Ph), 151.61 ($\text{C}2$), 164.80 ($\text{C}4$), 173.86° (COO)
Mass (matrix NOBA): $\text{C}_{21}\text{H}_{26}\text{N}_3\text{O}_8\text{P}$: 127 (thymine H^+ , 28), 479 (M^+ , 3), 480 (MH^+ , 59), 481 (MH^+ , ^{13}C , 17), 501 (MNa^+ , 3), 502
20 503 (MHNa^+ , 59), 503 (MHNa^+ , ^{13}C , 16)

High Resolution MS: found 480.1486 (MH^+), $\text{C}_{21}\text{H}_{27}\text{N}_3\text{O}_8\text{P}$ requires 480.1536

HPLC: RT 23.90, 24.33 mins (1:1)

2', 3'-Dideoxy-2', 3'-didehydrothymidine-5'-(phenyl methoxy-

2-aminoisobutylrlyl) phosphate

Cf 1200

Yield = 36%

5 ^{31}P (CDCl_3): 2.38, 3.05 (3:1)
 ^1H (CDCl_3): 1.53° (s, 6H, CMe_2), 1.91° (s, 3H, 5- CH_3), 3.71 (s, 3H, OCH_3), 4.31 (m, 2H, $\text{H}5'$), 4.23-4.41 (m, 3H, $\text{H}4'$ and $\text{H}5'$), 5.03 (bs, 1H, P-NH) 5.89° (m, 1H, $\text{H}2'$), 6.28° (m, 1H, $\text{H}3'$), 6.99-7.31 (m, 7H, Ph, HO and $\text{H}1'$), 9.09 (bs, 1H, base NH)
 ^{13}C (CDCl_3): 14.27 (5- CH_3), 28.74° (CMe_2), 54.81° (OCH_3), 58.88°
35 (CMe_2), 69.03° (d, C' , J = 5.58 Hz), 86.57° (d, J = 7.88 Hz, $\text{C}4'$), 91.51° ($\text{C}1'$), 113.24° ($\text{C}5$), 122.01° (d, J = 4.95 Hz, ortho-Ph), 126.88 ($\text{C}2'$), 129.25° (para-Ph), 131.57° (meta-
Ph), 135.19° ($\text{C}6$), 137.68° ($\text{C}3'$), 152.52° (d, J = 3.09 Hz, ortho-Ph), 153.05 ($\text{C}2$), 166.12 ($\text{C}4$), 177.69° (COO)

MS (matrix NOBA): 354 ((MH - thymine)⁺, base peak), 479 (M⁺, 3), 480 (MH⁺, 64), 481 (MH⁺, ¹³C, 17), 482 (MH⁺, 2 x ¹³C, 3), 502 (MNa⁺, 92), 503 (MHN₂⁺, 24)

High Resolution MS: found 480.1503 (MH⁺), C₂₁H₂₇N₃O₈P requires

5 480.1536

HPLC: RT 24.79, 25.29 mins (1:1)

2', 3'-Dideoxy-2', 3'-didehydrothymidine-5'-(phenyl methoxy-6-aminocaproyl) phosphate

10 Cf 1199

Yield = 80%

³¹P (CDCl₃): 6.90, 6.30 (1:1)

¹H (CDCl₃): 1.28 (s, 2H, CH₂ caproyl), 1.45 (m, 2H, CH₂ caproyl), 1.58 (m, 2H, CH₂ caproyl), 1.82^o (s, 3H, 5-CH₃), 2.28 (m, 2H, CH₂ caproyl), 2.87 (m, 2H, CH₂ caproyl), 3.65 (s, 3H, OCH₃), 3.81 (m, 1H, H4'), 4.25 (m, 2H, H5'), 4.95 (bs, 1H, NH caproyl), 5.86^o (m, 1H, H2'), 6.31^o (m, 1H, H3'), 6.98 (m, 1H H1'), 7.04-7.38^o (m, 6H, Ph and H6), 10.12 (bs, 1H, base NH)

20 ¹³C (CDCl₃): 13.47^o (5-CH₃), 25.43^o (CH₂ caproyl), 27.04^o (CH₂ caproyl), 32.15^o (CH₂ caproyl), 34.85 (CH₂ caproyl), 42.30^o (CH₂ caproyl), 52.61 (OCH₃), 67.92^o (C5'), 85.80 (d, J = 8.22 Hz), 90.68^o (C4'), 112.25^o (C5), 121.17^o (d, J = 4.58 Hz, ortho-Ph), 125.99 (C2'), 128.40^o (para-Ph), 130.77 (meta-Ph), 134.38^o (C6), 137.09^o (C3'), 151.69^o (d, J = 3.23 Hz, ortho-Ph), 152.26 (C2'), 165.36 (C4'), 175.07 (COO)

MS (matrix C1): 127 (thymineH⁺, 42), 508 (MH⁺, 18), 509 (MH⁺, ¹³C, 5)

High Resolution MS: found 508.1850 (MH⁺), C₂₃H₃₁N₃O₈P requires

30 508.1849

HPLC: RT 26.33 mins

2', 3'-Dideoxy-2', 3'-didehydrothymidine-5'-(β -alaninyl) phosphate ammonium salt

35 Cf1216

Yield = 62%

³¹P (D₂O): 8.84

¹H (D₂O): 1.73 (3H, s, 5-CH₃), 2.18 (2H, m, ala CH₂), 2.65 (m, 2H, ala CH₂), 3.79 (2m, H, H5'), 4.95 (m, 1H, H4'), 5.76 (m,

1H, H2'), 6.35 (m, 1H, H3'), 6.82 (m, 1H, H1'), 7.47 (s, 1H, H6)

¹³C (D₂O): 11.81 (5-CH₃), 38.51 (ala CH₂), 39.45 (d, ala CH₂, J = 6.64 Hz), 65.41 (d, C5', J = 4.91 Hz), 86.40 (d, J = 9.20 Hz, C4'), 90.20 (C1'), 111.07 (C5), 125.40 (C2'), 134.66 (C3'), 138.54 (C6), 152.53 (C2), 167.00 (C4), 181.04 (COO)

HPLC: RT = 32.74 mins.

10 2', 3'-Dideoxy-2', 3'-didehydrothymidine-5' (γ - aminobutylryl) phosphate ammonium salt

Cf 1224

Yield = 54%

³¹P (D₂O): 10.03

15 ¹H (D₂O): 1.47 (m, 2H, GABA CH₂), 1.72 (s, 3H, 5-CH₃), 1.98 (m, 2H, GABA CH₂), 2.48 (m, 2H, GABA CH₂), 3.72 (m, 2H, H5'), 4.91 (m, 1H, H4'), 5.72 (m, 1H, H2'), 6.26 (m, 1H, H3'), 6.72 (m, 1H, H1'), 7.45 (s, 1H, H6').

¹³C (D₂O): 11.79 (5-CH₃), 27.99 (d, J = 7.25 Hz, GABA CH₂), 34.47 (GABA CH₂), 41.17 (GABA CH₂), 65.35 (d, J = 4.68 Hz, C5'), 86.38 (d, J = 9.36 Hz, C4'), 90.27 (C1'), 111.47 (C5'), 125.29 (C2'), 134.70 (C3'), 138.68 (C6), 152.47 (C2), 166.95 (C4), 182.32 (COO)

25 2', 3'-Dideoxy-2', 3'-didehydrothymidine-5'-(caproyl) phosphate ammonium salt Cf 1217

Yield = 49%

³¹P (D₂O): 10.18

1H (D₂O): 1.01 (m, 2H, caproyl CH₂), 1.21 (m, 2H, caproyl CH₂), 1.32 (m, 2H, caproyl CH₂), 1.78 (s, 3H, 5-CH₃), 2.05 (m, 2H, caproyl CH₂), 2.58 (m, 2H, caproyl CH₂), 3.78 (m, 2H, H5'), 4.99 (s, 1H, H4'), 6.32 (m, 1H, H3'), 6.82 (m, 1H, H2'), 7.51 (s, 1H, H6)

¹³C (D₂O): 11.84 (5-CH₃), 25.66 (caproyl CH₂), 26.46 (caproyl CH₂), 31.10 (d, J = 6.82 Hz, caproyl CH₂), 37.06 (caproyl CH₂), 41.47 (caproyl CH₂), 65.37 (d, J = 4.83 Hz, C5'), 86.45 (d, J = 9.74 Hz, C4'), 90.29 (C1'), 111.43 (C5), 125.27 (C2'), 134.80 (C3'), 138.89 (C6), 152.48 (C2), 166.94 (C4), 183.15 (COO).

2', 3'-dideoxycytidine-5'-(phenyl-N-methoxylaninyl)
phosphoramidate Cf 1221

Yield = 16.6%

³¹P (CDCl₃): 3.94, 4.00

5 ¹H (CDCl₃): 1.33, 1.35 (2 x d, 3H, CH, ala); 1.92, 1.96, 2.41 (1H, 2H, 1H, 3 x m, H2', H3'); 3.66 (s, 3H, OMe); 3.86-4.35 (m, 5H, H4', H5', CH ala, NH ala); 5.63 (2 x d, J = 7.4 Hz, H6), 6.02 (m, 1H, H-1'), 7.12-7.32 (m, 5H, Ar), 7.73 (1H, 2 x d,

10 J = 7.4 Hz, H5)

¹³C (CDCl₃): 20.98 (CH, ala); 24.97, 25.11, 32.85 (C2', C3'); 50.12, 50.30 (CH, ala); 52.55 (OMe); 67.19, 67.26, 67.50 (C5'); 79.16, 79.27, 79.34 (C4'); 87.29, 87.46 (C1'); 93.48 (C5); 119.99, 120.04, 120.10, 125.05, 125.10, 129.73, 129.77

15 (CAr); 141.17 (C6); 150.48, 150.57 (C ipso Ar); 155.68 (C2); 165.44 (C4); 173.84, 173.94 (COala)

Mass (ES⁺): C₁₉H₂₅N₄O₇P: 475 (MNa⁺, 100); HPLC: RT = 20.53, 21.22 min

20 2', 3'-dideoxy-2', 3'-didehydrothymidine 5'
 -(phenylmethoxysarcosinyl phosphate) Cf 1098

Yield = 65%

³¹P (CDCl₃): 6.80, 7.36 ppm

¹H (CDCl₃): 1.72 (s, 3H, 5CH₃); 2.64, 2.67 (s, 3H, NCH₃); 3.62 (s, 3H, OCH₃); 3.40-4.10 (m, 2H, CH₂); 4.20-4.50 (m, 2H, H5'); 4.97 (bs, 1H, H4'), 5.80-5.90 (m, 1H, H2'); 6.30-6.40 (m, 1H, H3'); 6.97 (bs, 1H, H1'); 7.00-7.30 (m, 6H, Ar + H6); 9.59 (bs, 1H, NH)

¹³C (CDCl₃): 12.35 (5CH₃); 34.55-34.60-34.65 (NCH₃); 50.67-50.78-50.87 (CH₂); 52.10-52.13 (OCH₃); 62.27-66.77-66.82 (C5'); 84.71-84.84 (C4'); 89.52-89.82 (C1'); 111.16-111.33 (C5); 120-150 (m, Ar); 127.17-127.40 (C2'); 133.25-133.62 (C3'); 135.73-136.11 (C6); 150.85-150.90 (C2); 163.84-163.87 (C4); 170.57-170.60-170.84 (COOCH₃)

35 Mass : C₂₀H₂₄O₈N₃P : 488 ((M+Na)⁺, 100); 466 ((M+H)⁺, 5)

HPLC : RT = 25.17 and 25.59 min

2', 3'-dideoxy-2', 3'-didehydrothymidine 5'
 -(phenylethoxysarcosinyl phosphate) Cf 1133

Yield = 65%

³¹P (CDCl₃) : 0.87, 7.41 ppm

¹H (CDCl₃) : 1.18-1.24 (m, 2H, CH₃CH₂); 1.80 (s, 3H, 5CH₃); 2.68, 2.71 (s, 3H, NCH₃); 3.46-3.65 (m, 2H, NCH₂); 3.91-4.45

5 (m, 2H, H5'); 4.11, 4.13 (s, 3H, CH₂CH₃); 5.00 (bs, 1H, H4'); 5.82-5.88 (m, 1H, H2'); 6.33-6.37 (m, 1H, H3'); 7.00 (bs, 1H, H1'); 7.10-7.50 (m, 6H, Ar + H6); 8.75 (bs, 1H, NH)
¹³C (CDCl₃) : 12.86-12.89 (5CH₃); 14.69 (CH₂CH₃); 35.06-35.11 (NCH₃); 51.35-51.43-51.51 (NCH₂); 61.77 (CH₂CH₃); 66.77-67.27-10 67.33 (C5'); 85.26-85.36 (C4'); 90.01-90.31 (C1'); 111.69-111.86 (C5); 120-151 (m, Ar); 127.73-127.96 (C2'); 133.73-134.10 (C3'); 136.27-136.64 (C6); 151.61 (C2); 164.70 (C4); 170.62-170.66-170.85 (COOCH₃)

Mass : C₂₁H₂₆O₄N₃P : 502 ((M+ Na)⁺, 100); 480 ((M+H)⁺, 5)

15 HPLC : RT = 25.84 and 26.65 min

2', 3'-dideoxy-2', 3'-didehydrothymidine 5'-(methioninyl phosphate) Cf 1156

Yield = 52%

20 ³¹P (CDCl₃) : 7.77 ppm

¹H (CDCl₃) : 1.75-1.85 (m, 2H, CH₂S); 1.90 (s, 3H, SCH₃); 2.01, 2.10 (s, 3H, 5CH₃); 2.30-2.50 (m, 2H, CH₂CH₂S); 3.45-3.60 (m, 1H CHNH); 3.94 (s, 2H, H5'); 5.05 (bs, 1H, H4'); 5.90-6.00 (m, 1H, H2'); 6.40-6.50 (m, 1H, H3'); 6.93 (bs, 1H, H1'); 7.68 (s, 1H, H6)

¹³C (CDCl₃) : 11.91 (5CH₃); 14.46 (SCH₃); 29.58 (CH₂SCH₂CH₂); 34.69 (SCH₂CH₂); 56.42 (CHNH); 65.07-65.13 (C5'); 86.39-86.52 (C4'); 90.14 (C1'); 111.70 (C5); 125.48 (C2'); 134.77 (C3'); 138.91 (C6); 152.61 (C2); 167.18 (C4); 180.84 (COOH)

30 Mass : C₁₅H₂₂O₄N₃PS : 434 ((M-1), 100); 435 ((M), 15)

HPLC: RT = 31.38 min

2', 3'-dideoxy-2', 3'-didehydrothymidine 5'-(glycanyl phosphate) Cf 1163

35 Yield = 75%

³¹P (CDCl₃) : 11.72 ppm

¹H (CDCl₃) : 1.83 (s, 3H, 5CH₃); 3.29 (d, CH₂, J = 7.9Hz); 3.85-3.92 (m, 2H, H5'); 5.00 (s, 1H, H4'); 5.85-5.88 (m, 1H, H2'); 6.38-6.41 (m, 1H, H3'), 6.88-6.90 (bs, 1H H1'); 7.54

(s, 1H, H6)

¹³C (CDCl₃) : 19.09 (5CH₃); 52.24 (CH₂); 72.74-72.81 (C5'); 93.61-93.73 (C4'); 97.57 (C1'); 119.08 (C5); 132.80 (C2'); 141.89 (C3'); 145.74 (C6); 159.87 (C2); 174.34 (C4); 186.03-

5 186.15 (COOH)

Mass : C₁₂H₁₆O₈N₃P : 360 ((M-1), 100); 361 ((M), 15)

HPLC : RT = 32.57 min

2', 3'-dideoxy-2', 3'-didehydrothymidino 5'

10 -(phenylmethoxyisoleucinyl phosphate) Cf 1186

Yield = 82%

³¹P (CDCl₃) : 4.59, 5.16 ppm¹H (CDCl₃) : 0.91-0.99 (m, 6H, CH₃ + CH₂); 1.09-1.26 (CHCH₃); 1.28-1.56 (m, 2H, CH₂); 1.92, 1.97 (s, 3H, 5CH₃); 3.60-3.77

15 (m, 1H, CHNH); 3.77 (s, 3H, OCH₃); 3.88-3.99 (m, 1H, NHCH); 4.30-4.52 (m, 2H, H5'); 5.11-5.13 (m, 1H, H4'); 5.95-6.00 (m, 1H, H2'); 6.35-6.45 (m, 1H, H3'); 7.10-7.13 (m, 1H, H1'); 7.16-7.45 (m, 6H, Ar + H6); 8.68 (bs, 1H, NH)

¹³C (CDCl₃) : 11.90-11.92 (CH₂CH₃); 12.76-12.81 (5CH₃); 15.64

20 (CHCH₃); 25.06-25.14 (CH₂CHCH₃); 39.39-39.47-39.52-39.60 (CH₂); 52.61 (OCH₃); 59.38-59.54 (NHCH); 66.94-67.58-67.65 (C5'); 84.91-85.04-85.16 (C4'); 89.94-90.21 (C1'); 111.75-111.87 (C5'); 120-151 (m Ar); 127.82-127.87 (C2'); 133.49-133.69 (C3'); 135.99-136.28 (C6); 151.37 (C2); 164.40 (C4);

25 173.53-173.59-173.64 (COOCH₃)Mass: C₂₃H₃₀O₈N₃P : 529.91 ((M + Na)⁺, 100)

HPLC : RT = 30.52 and 31.14 min

2', 3'-dideoxy-2', 3'-didehydrothymidine 5'-(phenylalaninyl

30 phosphate) Cf 1187

Yield = 68%

³¹P (CDCl₃) : 7.58 ppm¹H (CDCl₃) : 1.70 (s, 3H, 5CH₃); 2.64-2.80 (m, 2H, CH₂Ph);

35 3.57-3.64 (m, 1H, CHNH); 3.68-3.70 (m, 2H, H5'); 4.85 (s, 1H, H4'); 5.73-5.75 (m, 1H, H2'); 6.26-6.29 (m, 1H, H3'); 6.74-6.75 (m, 1H, H1'); 7.02-7.28 (m, 5H, CH₂Ph); 7.44 (s, 1H, H6)

¹³C (CDCl₃) : 11.88 (5CH₃); 40.92-40.97 (CH₂ ala); 58.27 (CH

ala); 65.22-65.28 (C5'); 86.36-86.49 (C4'); 90.22 (C1'); 111.63 (C5); 125.38 (C2'); 126-129 (m, Ar); 134.74 (C3'); 138.31-138.48 (C6); 152.40 (C2); 166.81 (C4); 180.87-180.96 (COOH)

5 Mass : $C_{19}H_{22}O_8N_3P$: 450 ((M-1), 100); 451 ((M, 20)
HPLC : RT = 32.11 min

2', 3'-dideoxy-2',3'-didehydrothymidine 5'-(valinyl phosphate) Cf 1190

10 Yield = 67%

^{31}P (CDCl₃) : 8.35 ppm

1H (CDCl₃) : 0.72 (t, 6H, (CH₃)₂CH, J = 7.3 Hz); 1.62-1.73 (m, 1H, (CH₃)₂CH); 1.77 (s, 3H, 5CH₃); 3.12 (dd, 1H, NHCH, J = 5.6 Hz and 9.4 Hz); 3.80 (dd, 2H, H5', J = 3.5 Hz and 4.4 Hz); 4.92 (s, 1H, H4'); 5.76-5.78 (m, 1H, H2'); 6.31-6.35 (m, 1H, H3'); 6.79-6.81 (m, 1H, H1'); 7.53 (s, 1H, H6)
 ^{13}C (CDCl₃) : 11.84 (5CH₃); 17.95-18.84 ((CH₃)₂CH); 32.30-32.38 ((CH₃)₂CH); 62.43 (CHNH); 65.18-65.24 (C5'); 86.43-86.58 (C4'); 90.25 (C1'); 111.65 (C5); 125.20 (C2'); 134.90 (C3'); 138.73 (C6); 152.52 (C2); 167.05 (C4); 181.27-181.31 (COOH)

Mass : $C_{15}H_{22}O_8N_3P$: 402 ((M-1), 100); 403 ((M), 30)
HPLC : RT = 31.90 min

2', 3'-dideoxy-2', 3'-didehydrothymidine 5'-(leucinyl phosphate) Cf 1192

Yield = 83%

^{31}P (CDCl₃) : 7.98 ppm

1H (CDCl₃) : 0.71 (d, 6H, (CH₃)₂CH, J = 6.5 Hz); 1.22-1.34 (m, 2H, CH₂); 1.34-1.71 (m, 1H, (CH₃)₂CH); 1.80 (s, 3H, 5CH₃); 3.30-3.38 (m, 1H, CHNH); 3.82-3.85 (m, 2H, H5'); 4.95 (s, 1H, H4'); 5.80-5.82 (m, 1H, H2'); 6.35-6.37 (m, 1H, H3'); 6.81-6.82 (m, 1H, H1'); 7.58 (s, 1H, H6)

^{13}C (CDCl₃) : 12.53 (5CH₃); 22.88-22.99 ((CH₃)₂CH); 25.28 (CH₂); 45.27-45.34 ((CH₃)₂CH); 56.38 (CHNH); 65.74-65.81 (C5'); 87.12-87.25 (C4'); 90.89 (C1'); 112.30 (C5); 125.99 (C2'); 135.49 (C3'); 139.44 (C6); 153.12 (C2); 167.70 (C4); 183.36-183.42 (COOH)

Mass : $C_{16}H_{24}O_8N_3P$: 416 ((M-1), 100); 417 ((M, 20)
HPLC : RT = 35.02 min

2', 3'-dideoxy-2', 3'-didehydrothymidine 5'-
(phenylmethoxyalaninyl phosphate) [fast diastereoisomer] Cf
1193

³¹P (CDCl₃) : 4.51 ppm

5 ¹H (CDCl₃) : 1.25-1.40 (m, 3H, CHCH₃); 1.86-1.90 (m, 3H, 5CH₃); 3.74-3.90 (m, 4H, OCH₃ + CH ala); 4.37-4.47 (m, 2H, H5'); 5.08 (bs, 1H, H4'); 5.91-5.93 (m, 1H, H2'); 6.38-6.41 (m, 1H, H3'); 7.07-7.09 (m, 1H, H1'); 7.20-7.39 (m, 6H, Ar + H6); 9.04 (bs, 1H, NH)

10 ¹³C (CDCl₃) : 10.85 (5CH₃); 19.38-19.45 (CH₂CH₃); 48.71 (CHCH₃); 51.14 (OCH₃); 64.91-64.97 (C5'); 83.11-83.22 (C4'); 88.03 (C1'); 109.77 (C5); 118-149 (m, Ar); 125.84 (C2'); 131.88 (C3'); 134.44 (C6); 149.34 (C2); 162.35 (C4); 172.53-172.62 (CO ala)

15

2', 3'-dideoxy-2', 3'-didehydrothymidine 5'-
(phenylprolinyl phosphate) Cf 1194

Yield = 41%

³¹P (CDCl₃) : 5.27 ppm

20 ¹H (CDCl₃) : 1.55 (s, 3H, 5CH₃); 1.56-2.15 (m, 4H, CHCH₂CH₂); 3.10-3.30 (m, 2H, NCH₂); 3.90-4.00 (m, 1H, NCH); 4.20-4.50 (m, 2H, H5'); 5.11 (s, 1H, H4'); 5.89-5.91 (m, 1H, H2'); 6.41-6.44 (m, 1H, H3'); 6.76-6.78 (m, 1H, H1'); 6.99-7.40 (m, 6H, Ar + H6)

25 ¹³C (CDCl₃) : 11.84 (5CH₃); 25.44-25.56 (CH₂CH₂N); 31.94-32.06 (CH₂CHN); 47.40-47.46 (NCH₂); 63.31 (CHN); 67.14-67.21 (C5'); 85.56-85.68 (C4'); 90.69 (C1'); 111.00 (C5), 120-150 (m, Ar), 125.07 (C2'), 134.13 (C3'), 138.26 (C6), 152.67 (C2), 166.64 (C4), 181.32 (COOH)

30 Mass : C₂₁H₂₄O₈N₃P : 476 ((M-1)⁺, 100); 477 ((M)⁺, 25)

HPLC : RT = 34.16 min

1001 2', 3'-dideoxy-2', 3' didehydroadenosine-5'-
(phenylmethoxyalaninyl phosphoramidate):

35 Yield = 67%

¹H (dmso-d6): 8.14 (1H, s, H8), 8.06 (1H, d, H2), 7.07-7.40 (7H, m, Phe-H & NH₂), 6.93 (1H, s, H1'), 6.47 (1H, 2d, H3'), 6.21 (1H, d, H3'), 5.96 (1H, m, NH), 5.11 (1H, m, H4'), 4.10 (2H, m, H5'), 3.5-4.83 (1H, 2m, CH ala), 3.52 (3H, d, MeO),

1.08 (3H, 2d, CH, ala).
³¹P (dmso-d6): 4.92, 4.78.
¹³C (dmso-d6): 172.909-172.815 (CO ala), 154.663 (C-2),
152.238 (C-6), 149.524-149.442 (Ar-ipso), 148.782 (C-4),
5 138.006-137.907 (C-8), 132.286-132.205 (C-2'), 128.621 (Ar-
meta), 125.384-125.210 (Ar para), 123.928 (C-3'), 119.067-
119.00 (Ar ortho), 118.508 (C-5), 87.311-87.060 (C-1'),
84.485-84.368 (C-4'), 66.093-65.324 (C-5'), 51.477-51.429
(OMe), 49.109-48.989 (C-H ala), 19.903-19.585 (CH, ala).
10 Mass. Calculated MH⁺: 475.149. Found: 475.151

1093 2', 3'-dideoxy adenosine 5'-(phenyl methoxyalaninyl) phosphoramidate

Yield = 42%

15 ¹H (CDCl₃) : 8.32 (1H, s, H-8), 8.12 & 8.11 (1H, 2s, H-2),
7.22 (5H, m, Ar), 6.40 (2H, 2bs, NH₂), 6.30 (1H, t, H-1',
J = 5.4 Hz), 4.42 (4H, m, N-H, 2H5' & H4'), 4.00 (1H, 2d,
Ala C-H), 3.65 (3H, 2s, OMe), 2.52 (2H, m, H3'), 2.13 (2H,
m, H2'), 1.31 (3H, 2d, CH, ala, J = 7.3 Hz).
20 ³¹P (CDCl₃) : 4.26, 4.19.
¹³C nmr (CDCl₃) : 174.534, 174.468, 174.441, 174.372 (O-C=O),
156.148 (C-2), 153.331 (C-6), 151.092 & 151.006 (2 Ar ipso),
149.674 & 149.599 (C-4), 139.211 & 139.103 (C-8), 130.040
(Ar meta), 125.325 (Ar para), 120.570 (C-5), 120.508 &
25 120.327 (Ar ortho), 85.994 & 85.746 (C-1'), 80.105, 79.985
& 79.874 (C-4'), 68.136, 68.067, 67.704 & 67.636 (C-5'),
52.868 (OMe), 50.628 & 50.531 (Ala C-H), 32.712 (C-2'),
26.339 & 26.106 (C-3'), 21.337, 21.264 & 21.190 (CH, ala).
Mass: Calculated MH⁺: 477.165. Found: 477.164.

30

1094 2', 3'-dideoxy-2', 3' didehydroadenosine 5'-(phenyl benzylalaninyl) phosphoramidate:

Yield = 65%

¹H (CDCl₃): 8.32 (1H, bs, H-8), 7.99 (1H, bs, H-2), 7.21
35 (11H, m, Ar-H & H1'), 6.34 (1H, m, H3'), 6.07 (1H, m, H2'),
5.81 (2H, 2bs, NH₂), 5.08 (3H, 2bs, Bz-CH₂ & H4'), 4.05 (4H,
m, NH, CH, H5'), 1.24 (3H, 2d, methyl ala, J = 6.9 Hz).
³¹P (CDCl₃): 4.21, 3.98
¹³C (CDCl₃): 173.700 & 173.601 (O-C=O), 156.005 (C-2),

153.728 (C-6), 150.952 & 150.870 (Ar), 150.322 & 150.280 (C-4), 139.484 & 139.368 (C-8), 135.672 (Ar), 133.733 & 133.654 (C-2'), 130.066 (Ar), 129.041, 128.895, 128.635 & 128.601 (Ar), 126.751 & 126.598 (C-3'), 125.375 (Ar), 120.529, 5 120.463, 120.399, 120.119 & 120.051 (C-5 & Ar), 88.702 & 88.476 (C-1'), 85.907, 85.476, 85.791 & 85.736 (C-4'), 67.632, 67.475 & 67.403 (C-5' and Bz-CH₂), 66.805 & 66.745 (C-5'), 50.677 & 50.542 (Ala C-H), 21.399, 21.335, 21.083 & 21.019 (methyl Ala).

10 Mass: Calculated MH⁺: 551.181. Found: 551.179.

1168 2', 3'-dideoxy-2', 3'-didehydroadenosine 5'-alaninyl phosphoramidate

Yield = 69%

15 ¹H nmr (D₂O): 8.09 (1H, s, H8), 7.88 (1H, s, H2), 6.81 (1H, s, H1'), 6.33 (1H, d, H3'), 6.02 (1H, d, H3'), 5.01 (1H, m, H4'), 4.73 (2H, m, H5'), 3.5-4.83 (1H, 2m, CH ala), 0.89 (3H, 2d, CH₃, ala).
³¹P (D₂O): 8.34.

20 ¹³C (D₂O): 183.055 (CO ala), 155.549 (C-2), 152.745 (C-6), 148.643 (C-3), 140.928 (C-8), 134.730 (C-2'), 124.709 (C-3'), 118.527 (C-5), 88.299 (C-1'), 87.199 & 87.073 (C-4'), 65.215-65.149 (C-5'), 52.564 (Ala C-H), 21.435-21.381 (Ala CH₃).

25

1196 - 2', 3'-Dideoxy-2', 3'-didehydrothymidine-5'-(phenyl dimethoxy glutaminyl phosphoramidate

Yield 33%

³¹P (CDCl₃) 4.14, 4.76

30 ¹H (CDCl₃) 1.81, 1.85 (5CH₃); 1.91-2.18 (m, 2H, CH₂ Gln); 2.24-2.36 (m, 2H, CH₂ Gln); 3.64 (s, 3H, NMe); 3.69 (s, 3H, OMe); 3.92-4.21 (m, 2H, H5'); 4.23-4.42 (m, 2H, CH Gln, NH Gln); 5.00 (m, 1H, H4'); 5.91 (m, 1H, H2'); 6.31 (m, 1H, H3'); 7.01 (m, 1H, H1'), 7.03-7.34 (m, 6H, Ph, H6); 9.49 (s, 35 1H, NH)

¹³C (CDCl₃) 12.32-12.36 (5CH₃); 29.01-29.42 (CH₂ Gln); 29.46 (NMe); 51.81 (CH Gln); 52.65 (OMe); 53.65-53.92 (CH₂ Gln); 66.63-67.33 (C5'); 84.48-84.71 (C4'); 89.57-89.83 (C1'); 111.29-111.44 (C5); 119.98-120.22 (Ph); 125.21-125.26 (Ph);

127.39-127.50 (C2'); 129.74-129.78 (Ph); 133.00-133.25 (C3'); 135.60-135.90 (C6); 150.98 (C2); 164.00-164.09 (C4); 172.96-173.23 (CO, CON)
 Mass (ES) : $C_{23}H_{29}N_4O_9P$: 536 (M^+ , 100); 537 (MH^+ , 32)

5

1214 - 2', 3'-Dideoxy-2', 3'-didehydrothymidine-5'-(phenyl dimethoxy asparaginyl) phosphoramidate

Yield 75%

^{31}P (CDCl₃) 1.15, 2.20

10 1H (CDCl₃) 1.81, 1.86 (s, 3H, 5CH₃); 2.49-2.92 (m, 2H, CH₂ Asn); 3.64 (s, 3H, NMe); 3.72 (s, 3H, OMe); 4.04-4.26 (m, 2H, H5'); 4.28-4.43 (m, 2H, CH Asn, NH Asn); 5.05 (m, 1H, H4'); 5.89 (m, 1H, H2'); 6.31 (m, 1H, H3'); 7.01 (m, 1H, H1'); 7.14-7.33 (m, 6H, Ph, H6); 8.46 (s, 1H, NH)
 15 ^{13}C (CDCl₃) 12.28 (5CH₃); 51.01 (CH Asn); 52.09 (OMe); 52.94 (CH₂ Asn); 84.75 (C4'); 89.60 (C1'); 111.30 (C5); 125-130 (Ph); 127.32-127.48 (C2'); 133.10-133.41 (C3'); 135.94 (C6)
 Mass (ES) : $C_{22}H_{27}N_4O_9P$: 522 (M^+ , 100); 523 (MH^+ , 31)

20 1215 - 2', 3'-Dideoxy-2', 3'-didehydrothymidine-5'-(phenyl methoxytryptophanyl) phosphoramidate

Yield 100%

^{31}P (CDCl₃) 4.15, 4.57

1H (CDCl₃) 1.74 (s, 3H, 5CH₃); 3.16 (m, 2H, CH₂ Trp); 3.60 (s, 3H, OMe); 3.75-4.05 (m, 2H, H5'); 4.10-4.33 (m, 2H, CH Trp NH Trp); 4.84 (m, 1H, H4'); 5.79 (m, 1H, H2'); 6.15 (m, 1H, H3'); 6.86 (m, 1H, H1'); 6.91 (m, 1H, H6); 7.00-7.49 (m, 10H, Ar); 8.45 (s, 1H, NH Trp); 9.14 (s, 1H, NH)
 ^{13}C (CDCl₃) 14.75 (5CH₃); 32.46 (CH₂ Trp); 54.91 (CH Trp);
 30 57.53-57.61 (OMe); 69 (C5'); 87.06 (C4'); 92.03-92.25 (C1'); 111.63 (C5); 127.60 (C2'); 135.45-135.83 (C3'); 138.11-138.62 (C6); 152.78-153.41 (C2); 166.28-166.40 (C4); 175.85 (CO)
 Mass (ES) : $C_{28}H_{28}N_4O_9P$: 579 (M^+ , 100); 580 (M^+ , 43)

35

462 3'-Deoxy-3'- β -azidothymidine 5'-(phenyl methoxylalaninyl) phosphoramidate

1H (CDCl₃) : 1.39 (d, 3H, J = 7.2 Hz, CH, ala), 1.94 (s, 3H 5-

Me), 2.15 (d, 1H, J = 15.5 Hz, H2'), 2.68-2.79 (m, 1H, H2'), 3.72 (s, 3H, OMe), 3.90-4.50 (m, 6H, H3' + H4' + H5' + NH + CHala), 6.18 (dd, 1H, J = 7.5 and 3.1 Hz, H1'), 7.1-7.4 (m, 6H, Ph + H6), 8.82 (bs, 1H, NH).

5 ^{13}C (CDCl_3) : 12.67 (5-Me), 20.96, 21.29 (ala-Me), 38.50 (C2'), 50.16, 50.28 (CHala), 52.57 (OMeala), 60.74 (C3'), 64.43 (C5'), 80.17 (C4'), 83.93 (C1'), 111.21 (C5), 120.11 (Ar2), 125.18 (Ar4), 129.73 (Ar3), 135.18 (C6), 159.96 (Ar1), 150.30 (C4), 163.49 (C2), 173.84 (COala).

10 ^{31}P (CDCl_3) : 1.55

IR (CDCl_3): 3216, 2113, 1685 cm^{-1} .

Mass 509.1543 (MH^+ , 40%, calculated 509.1549), 340(12), 250(17), 200(18).

HPLC: RT = 28.48 min.

15

536 3'-Deoxy-3' β -azidothymidine 5'-(m-trifluoromethylphenyl methoxylalaninyl) phosphoramidate

^1H (CDCl_3): 1.39, 1.40 (d, 3H, J = 7.2 Hz, Me-ala), 1.92, 1.93 (s, 3H, 5-CH₃), 2.15 (d, 1H, J = 15.1 Hz, H2'), 2.71-20 2.80 (m, 1H, H2'), 3.70, 3.71 (s, 3H, OMe), 3.90-4.50 (m, 6H, H3' + H4' + H5' + NH + CHala), 6.19 (dd, 1H, J = 7.7 and 3.3 Hz, H1'), 7.41-7.46 (m, 5H, Ph + H6), 9.52 (bs, 1H, NH).

^{13}C (CDCl_3): 12.58 (5-Me), 20.75, 20.83 (CH, ala), 38.33, 38.44 (C2'), 50.15, 50.29 (CHala), 52.55 (OMeala), 60.77 (C3'), 64.72 (C5'), 80.05, 80.35 (d, J = 6.8 Hz, C4'), 83.94 (C1'), 111.25 (C5), 117.43 (Ar2), 121.81, 121.86 (Ar4), 123.37 (q, J = 273 Hz, CF₃), 123.74 (Ar6), 130.35 (Ar5), 132.11 (q, J = 33 Hz, Ar3), 135.11 (C6), 150.49 (C4), 150.62 (Ar1), 163.78 (C2), 173.68, 173.87 (d, J = 7.8 Hz, COala).

30 ^{31}P : 2.69

Mass 577 (MH^+ , 40%) 340 (13), 268 (14), 250 (12).

HPLC: RT = 30.66 min.

550 3'-Deoxy-3' β -azidothymidine 5'-(3, 5-dichlorophenyl methoxylalaninyl) phosphoramidate

^1H (CDCl_3): 1.42 (d, 3H, J = 6.8 Hz, Me-ala), 1.94, 1.95 (d, 3H, J = 1.2 Hz, 5-CH₃), 2.17, 2.18 (d, 1H, J = 15.1 Hz, H2'), 2.76-2.85 (m, 1H, H2'), 3.74, 3.75 (s, 3H, OMe), 3.90-4.50 (m, 6H, H3' + H4' + H5' + NH + CHala), 6.20 (dd, 1H, J

= 7.7 and 3.3 Hz, H1'), 7.19 (m, 2H, Ar2), 7.27 (s, 1H, Ar4), 7.41, 7.42 (s, 1H, H6), 9.04 (bs, 1H, NH).
¹³C: 12.65 (5-Me), 20.85, 20.91 (CH, ala), 38.38, 38.48 (C2'), 50.18, 50.29 (CHala), 52.68 (OMeala), 60.77 (C3'), 5 64.86, 64.93 (C5'), 79.80, 80.20 (d, J = 8Hz, C4'), 83.97 (C1'), 111.35 (C5), 117.28, 119.38 (d, J = 6Hz, Ar2), 125. 58 (Ar4), 135.10 (C6), 135.46, 135.50 (Ar3), 145.35 (Ar1), 150.36 (C4), 163.61 (C2), 173.64, 173.79 (COala).
³¹P: 2.83
10 Mass 577, 579, 581 (MH⁺ 5:3:1:) 307, 309, 311 (12:8:2) 289
(10)

In vitro Testing

Cells were infected with HIV-1 as previously described 5 [Balzarini *et al.* AIDS (1991), 5, 21-28]. Briefly, 5 x 10⁵ cells per milliliter were infected with HIV-1 or HIV-2 at 100 CCID₅₀ (50% cell culture infective dose) per milliliter of cell suspension. Then 100 μ L of the infected 10 cell suspension was transferred to microtiter plate wells and mixed with 100 μ L of the appropriate dilutions of the test compounds. After 4 days giant cell formation was recorded microscopically in the HIV-infected cell cultures [CEM], and after 5 days the number of viable cells was determined by trypan blue staining of the HIV-infected cell 15 cultures [MT4]. The 50% effective concentration (EC₅₀) and 50% cytoxic concentration (CC₅₀) were defined as the compound concentrations required to reduce by 50% the number of giant cells or viable cells in the virus-infected and mock-infected cell cultures, respectively.

20

The anti-HIV-1 activities and toxicities of compounds were also assessed in two cell lines:

C8166 cells. Cells were grown in RPMI 1640 with 10% calf 25 serum. 4 x 10⁴ cells per microtiter plate well were mixed with 5-fold dilutions of compound prior to addition of 10 CCID₅₀ units of III-B strain of HIV-1 and incubated for 5-7 days (Betbeder *et al.* Antiviral Chem. Chemoth. 1, 241-247, 1990). Formation of syncytia was examined from 2 days post- 30 infection. Culture fluid was collected at 5-7 days and gp120 antigen production measured by ELISA (Mahmood and Hay, J. Immunol. Meth., 151, 9-13, 1992). The EC₅₀ is that concentration of drug [in μ M] required to reduce gp120 production by 50%. Cell viability of infected and 35 uninfected cells were assessed by the MTT-Formazan method (Pauwels *et al.* J. Virol. Meth. 20, 309-321, 1988).

JM cells JM cells, which are relatively resistant to the antiviral effects of AZT and a number of its derivatives,

were infected with HIV-1 strains and the antiviral and toxic effects of compounds assessed as for C8166 cells. Both GB8 or IIIB strains of HIV1 were used, with no detectable differences in the end-points noted.

5

Each assay was carried out in duplicate, on at least two separate occasions, and data quoted are the average of each separate assay.

10 The compounds of the present invention have been shown to be active against both HIV1 and HIV2 in both TK⁺ and TK⁻ cells as illustrated in Table 2.

Table 2

15	HIV1 in C8166/JM			HIV2 in CEM TK ⁺ /CEM TK ⁻		
	Compound	EC ₅₀	μM	EC ₅₀	μM	EC ₅₀
		C8166	JM	CEM TK ⁺	CEM TK ⁻	
	730	0.0008	0.0008	0.016	0.06	
20	d4T (comparative)	0.08	0.8	1.2	>100	

As expected, d4T (comparative) loses activity in the kinase deficient cells (especially CEM TK⁻), whilst compound 730 of the invention retains good activity in both TK⁺ and TK⁻ 25 against both HIV1 and HIV2. Compound 730 of the invention is >1000 times more potent than d4T in TK⁻ cells. Surprisingly, the compound is 100-fold more potent than d4T in CEM TK⁻ assays.

30 The potent activity of the compounds of the invention is further supported by the data in Table 3, which illustrates activity, toxicity and selectivity index of a series of compounds of the present invention.

35 The enhanced anti-viral potency and reduced cytotoxicity of the phosphate derivatives lead to very large improvements in

The enhanced anti-viral potency and reduced cytotoxicity of the phosphate derivatives lead to very large improvements in selectivity index [defined as CC_{50}/EC_{50}] evidencing marked improvements in in vivo efficacy compared to d4T 5 (comparative).

Evidence that the compounds of the present invention are acting via a pathway different to that of d4T or AZT is provided by the data of Table 4.

10

As can be seen, whilst the potency of d4T (comparative) is much reduced in nucleoside resistant strains, the potency of the compounds of the present invention is largely maintained. Thus, it is clear that the compounds of the 15 present invention are not acting primarily via the conventional nucleoside 5' triphosphate derivative.

CEM and MT4 cells (at 400,000 cells/ml) and PBL cells (at 2,000,000 cells/ml) were exposed to different concentrations 20 of [3 H] 324 and incubated at 37°C for 24 hours. Then cells were washed twice with cold PBS and to the cell pellet was added 400 μ l cold methanol 66%. After standing on ice for 10 min, the cell extract was centrifuged and the supernatent analyzed on HPLC. As shown in Table 5, intracellular D4T- 25 MP (monophosphate) levels increased proportionally in function of the initial concentration of 324 in all three cell lines tested. However, the increase of D4T-TP (triphosphate) levels slowed down at initial 324 concentrations that were higher than 25 μ M (for CEM and MT4 30 cells) or higher than 1.0 μ M (for PBL). Surprisingly, a metabolite (designated X) accumulated substantially and predominantly in all three cell types. The accumulation was proportional to the initial 324 concentration, and, again, was lower in PBL than CEM and MT4 cells.

35

When 1mM 324 was incubated with high concentrations of hog liver esterase at 37°C in Tris-HCl buffer containing 5 mM MgCl₂, a time-dependent formation of a metabolite was observed. This metabolite co-eluted with the predominant

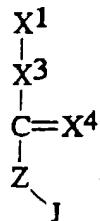
metabolite (X) that was found in the cell extracts after incubation of the intact cells with [³H] 324. metabolite X corresponds to a compound of formula (10), wherein Y is oxygen, X¹ is NH, X² is oxygen, B is thymine, R¹ is Me, R² is 5 hydrogen.

Data on an expanded range of compounds is presented in Table 6 (d4T analogues) and Table 7 (dideoxy and 3' - β - substituted nucleoside analogues) in which:-

10

Cpd and Init : refer to the compound reference numbers;
Y : refers to the group:-

15



20

Z : refers to the 3' - substituent on a deoxyribose sugar wherein the substituent is in an "o" orientation (R⁹) unless designated "up" which refers to a " β " orientation (R¹⁰);

30

B : refers to the heterocyclic nucleic acid base, present at C1' in β - orientation; conventional one-letter base codes are used; pyrimidine substituents are at C5.

The data columns are, in order:

HIV1 MT4: EC₅₀ in μ M for inhibition of HIV-1 in MT4 cells.

HIV2 MT4: EC₅₀ in μ M for inhibition of HIV-2 in MT4 cells.

35 CC50 MT4: CC₅₀ in μ M for toxicity to MT-4 cells.

HIV1 CEM: EC₅₀ in μ M for inhibition of HIV-1 in CEM cells.

HIV2 CEM: EC₅₀ in μ M for inhibition of HIV-2 in CEM cells.

HIV2 CEM-TK: EC₅₀ in μ M for inhibition of HIV-2 in CEM/TK cells.

CC50 CEM: CC₅₀ in μ M for toxicity to CEM cells.

EC50 MSV: EC₅₀ in μ M for inhibition of MSV

MCC MSV: Minimum cytotoxic concentration in MSV assay

5 Where data of table 6 differs from that presented in Tables 2 to 5, the data of the former relates to the mean result obtained from two or more repeat experiments, whereas the latter relates to individual experimental results.

Entry	Ar	R ¹	J	Activity EC ₅₀	Toxicity CC ₅₀ /EC ₅₀ x10 ³	Selectivity
						CC ₅₀ /EC ₅₀ x10 ³
323		4-EtPh	Me	Me 0.0032	50	15.6
324		Ph	Me	Me 0.0032	150	46.9
327		4-FPh	Me	Me 0.0032	200	62.5
526		3-CF ₃ Ph	Me	Me 0.0008	200	250
546		3,5-Cl ₂ Ph	Me	Me 0.001	100	100
730	Ph	Me	Bz1	0.0008	400	500
776	2,4-Br ₂ Ph	Me	Me	0.0008	100	125
779	F ₃ Ph	Me	Me	0.064	80	1.25
862	Ph	Me	Hex	0.0012	500	417
863	Ph	Me	Me	0.016	500	31.2
864	Ph	CH ₂ iPr	Me	0.016	>1000	>62.5
865	Ph	iPr	Me	0.8	>1000	>1.25
866	Ph	H	Me	0.8	>1000	>1.25
867	Ph	[CH ₂] ₂ SM ₂	Me	0.0016	>1000	>62.5
868	2,4-Br ₂ Ph	Me	Bz1	0.0032	500	156
877	Ph	Bz1	Bz1	0.0003	80	267
878	Ph	Bz1	tBu	0.16	150	0.9
892	Ph	Me	Cyclohex	0.0016	500	312
893	Ph	Me	tBu	0.2	>1000	>5.0
					0.08	0.6

[data are μ M for HIV1 in C8166 cells]
By comparison, similar data for d4T:
d4T

Table 4

Compound	EC ₅₀ in μM	EC ₅₀	SI	EC ₅₀	EC ₅₀	EC ₅₀	EC ₅₀
HIV RT	8166	8166		CEM	CEM TK	HeLa	HeLa
	HIV1	HIV1		HIV1	HIV2	HIV1	HIV1
					d4T-Sensitive	d4T-Resistant	
d4T	Inactive	0.08	625	0.5	>100	0.86	3.38
324	50	0.0032	62,500	0.18	0.08	n/d	n/d
526	n/d	0.0008	>250,000	0.08	0.06	0.04	0.05
546	n/d	0.001	>200,000	0.06	0.06	0.03	0.04
AZT	Inactive	0.008	>100,000	0.003	>100	n/d	n/d

Table 5

Metabolism of [³H] 324 after 24 hr incubation in human CEM, MT4 and PBL cells

Metabolite	nmole/10 ⁹ cells						PBL				
	Initial concentration of [³ H] 324 (μM)			MT-4							
	0.2	1.0	5.0	25	100	500	0.2	25	0.2	1.0	25
324 + D4T	7.6	47.8	228	897	4,333	16,691	7.9	1,255	2.0	12.2	245
D4T-MP	3.9	10.8	54	490	2,259	11,359	2.9	394	2.4	14.2	355
D4T-DP	1.5	5.1	21.6	75	214	430	2.0	116	0.45	1.8	15.3
D4T-TP	10.3	37.6	177	553	691	938	22.6	535	6.6	27	149
	1.33	628	3,164	16,193	66,359	204,442	117	14,582	17.6	97.3	1,995

Ctrl	AlO	Y	Z	B	UV1 M	UV2 M	CC50 M	UV1 CEM	UV2 CEM	2.CEM.1K	CC50 CEM	ESD MSV	CCMSV
268	AS							0.24	1.2	>100			
321	AS/II	IleO						>42	>42	>42		36	
322	AS	TCEO						29	71	59			
323	AS	E10						0.057	0.063	>100	0.07	0.16	60
324	AS/II	PhO						0.081	0.063	>100	0.075	0.075	100
325	AS	ICEO						0.44	0.5	>100	1	2	0.7
326	AS	P10						36	84	>250	>230	135	>250
345	AS	ICEO								8	11	10	
400	AS	ICEO								>40	>40	>40	
401	AS	ICEO								>210	>210	>210	
402	AS	ICEO								118	>204	161	
403	AS	TCEO								>216	>216	>216	
404	AS	ICEO								>209	>209	>209	
406	AS	ICEO								>203	>203	>203	
407	AS	TCEO								0.5	0.5	0.5	86
446	AS									>95	>95	>95	
479	SI	PrO								>258	>258	>258	
480	SI	BuO								>48	>48	>48	
481	SI	BuO								>9	>9	>9	
504	AS	TFEO								73	116	>226	
526	AS	MC3PhO								10	0.15	0.12	30
546	AS	J-5-Cl2PhO								10.5	0.12	0.12	26.9
547	AS	MFMPbO								>3520	>7	>35	
551	AS	E10								>58	>58	>58	
558	AS	PhO								>14	>14	>14	
561	AS	FPhO								85	4	7.72	
562	AS	ICEO								>36	>36	>36	
563	AS	E10								>268	>268	>268	
564	AS	E10								>48	>48	>48	>250
730	DC	PhO								0.016	0.016	0.06	25
740	DC	MeO						25.4	50.9	>350	20	50	>250
775	DC	HO								0.8	0.95	0.95	174
776	DC	2,4B1-2PhO								0.04	0.055	0.025	16
779	DC	FPhO								1.72	4.07	82	115
786	DC	IleO									0.9	0.5	30
787	DC	MeO1PhO									0.65	0.95	45
788	DC	E10									0.65	0.6	30
													115

TABLE 6

Cpd	Init	Ato	Y	Z	B	IIIIV1 M		IIIIV2 M		CCS50 M		IIIIV1 CEM		IIIIV2 CEM		2. CEM IX		CCS50 CEM		EC50 MSV	
						IIIIV1	IIIIV2	IIIIV1	IIIIV2	IIIIV1	IIIIV2	IIIIV1	IIIIV2	IIIIV1	IIIIV2	IIIIV1	IIIIV2	IIIIV1	IIIIV2	IIIIV1	IIIIV2
789	DC	DCdO	II		I					0.65	0.65	40	64								
790	DC	BuO	II		I					0.65	0.9	30	177								
791	DC	OctO	II		I					0.4	0.6	23	90								
792	DC	PhIO	II		I					0.55	0.9	40	137								
793	DC	PhO	II		I					0.65	0.65	33	170								
816	DC	C16O	II		I					0.65	0.65	15	25								
817	DC	MeO	II		I					0.7	0.55	20	146								
828	DC	PhIO	C12N11		I					>10	>10		14								
829	DC	PhO	C8N11		I					>10	>10		23								
830	DC	PhO	IIuN11		I					140	100	125	250								
849	DC	PhO	BzAlaN11		U					23	15	10	115								
853	DC	PhO	OH		I					0.65	0.7	23	153								
858	DC	PhO	PrN11		I					>250	>250		>250								
859	DC	PhO	IIuN11		I					>50	>50		>50								
860	DC	PhO	PrN111		I					>250	>250		>250								
861	DC	PhO	CNEO		I					1.2	0.95	17.5	250								
862	DC	PhO	IIuAlaN11		I					0.06	0.055	0.033	48								
863	DC	PhO	MePhenN11		I					0.2	0.4	34	0.8	1.35	0.33	216					
864	DC	PhO	MeBuN111		I					0.2	0.5	62	1.1	2.23	0.4	250					
865	DC	PhO	MeVaN111		I					3.6	11.2	>250	12.5	12.5	4	>250					
866	DC	PhO	MeOlyN111		I					1.3	6.7	>250	6	6	7	>250					
867	DC	PhO	MeMethN11		I					0.2	0.4	22	0.6	0.8	0.34	>250					
868	DC	Br2PhO	BrAlaN11		I						0.2	0.2	0.2	50							
870	DC	Br2PhO	BrAlaN11		U					>50	>50		12.5								
877	DC	PhO	DiPhenN11		I						0.6	0.6	0.24	44							
878	DC	PhO	IIuPhenN11		I						2	2	0.65	80							
879	DC	PhO	MePhenN11		I						>10	>10		42.5							
880	DC	PhO	PhO		I						25	25	75	>250							
881	DC	IIO	PhIAlaN11		I																
892	GOd	PhO	C1bAlaN11		I					0.063	0.075	0.09	51.4								
893	GOd	PhO	PhIAlaN11		I					0.85	1.1	0.74	>250								
932	ASs	PhO	Me D AlaN11		I						3	2	2.5	>250							
933	DC	PhO	NaPhenN11		I						35	12.5	>50	92	>100						
949	DC	PhO	ELMeN111		I						0.8	0.3	0.15	166	52	>100					
950	DC	PhO	EL1-AlaN11		I						250	>250	>250	>100	>100	>100					

TABLE 6 (CONTD.)

Cpd	Init	ArO	Y	Z	B	HIV1 M HIV2 M C550 M						HIV1 CEM HIV2 CEM C550 CEM						EC50 MSV MCCMSV					
						HIV1	HIV2	M	C550	M	HIV1	C550	HIV2	CEM	2.CEM	TK	EC50	MSV	MCCMSV				
951	DC	PhO	EtAla ^{III}	=	I	0.1	0.07	0.07	0.07	0.07	55	25	>100										
978	DC	PhO	MeLactO	=	I	40	50	>250	>250	>250	>100	>100											
979	DC	PhO	EtLactO	=	I	28	23	160	23	160	>250	>250											
980	DC	PhO	MeGlyctO	=	I	27.5	50	>250	>250	>250	>100	>100											
981	DC	PhO	EtGlycO	=	I	12.5	12.5	150	150	150	>250	>250											
982	DC	PhO	MeManO	=	I	1.7	0.65	15	15	15	94	14											
983	DC	M	MeEphedolin	heterocycle	=	>250	122	>250	>250	>250	>100	>100											
1078	SV	PhO	Me2AspNH	=	I	0.55	0.65	0.33	0.33	0.33	209	31.4	>100										
1079	SV	IIO	AspNH	=	I	1.8	2.5	70	70	70	>250	9.3	>100										
1080	SV	IIO	MeAspNH ^[1]SC]	=	I	3.5	5	110	2250	2250	30.3	30.3	>100										
1081	ASS	PhO	Me2GLuNH	=	I	8	5.33	1.6	1.6	1.6	>250	88.8	>100										
1083	ASS	IIO	GluNH	=	I	6.5	5.5	>250	>250	>250	54.6	54.6	>100										
1095	ASS	IIO	D-Ala ^{III}	=	I	1.3	1.6	10	10	10	>250	0.42	>100										
1129	SV	NO	MeAlaNH	=	I	2	4.5	50	50	50	>250	47.4	>100										
1131	SV	OH	OH	=	I	0.4	0.6	50	50	50	>250	6.7	>100										
1133	LB	PhO	EtGlycNMe	=	I	75	87.5	>250	>250	>250	>100	>100	>100										
1135	SV	MeO	BiAlaNH	=	I	10	15	17.5	17.5	17.5	>250	>250	>100	>100	>100	>100	>100	>100					
1137	SV	OH	BiAla ^{III}	=	I	0.95	1.6	8	8	8	>250	15.7	>100										
1139	MW	PhO	Oc10011	=	I	15	15	>50	>50	>50	>20	66.6	>20										
1155	LB	IIO	MeAla ^{III}	=	I	127	0.7	50	50	50	>250	16.2	>100										
1163	LB	IIO	GlyNH	=	I	2	5	130	130	130	>250												
1186	LB	PhO	Melle ^{III}	=	I																		
1187	LB	IIO	PheNH	=	I																		
1189	YW	PhO	ClxC12Ala ^{III}	=	I	0.04																	
1190	LB	OH	ValNH	=	I																		
1196	KI	PhO	MeGlualine ^{III}	=	I																		
1197	IWI	PhO	Me ^{[1]Ala} NH	=	I																		
1198	IWI	PhO	MeGABA ^{III}	=	I																		
1199	IWI	PhO	MeCapro ^{IV} NH	=	I																		
1200	IWI	PhO	MeOCOCMe2Ala	=	I																		
1214	KI	PhO	MeSpargagineN	=	I																		
1215	KI	PhO	MeTrypt ^{IV} NH	=	I																		
1216	IWI	OH	I ^{[1]Ala} NH	=	I																		

TABLE 6 (CONTD.)

Cpd	Init	ArO	Y	Z	B	HIV 1 M/HIV 2 M	CC50 M	HIV 1 CEM/HIV 2 CEM	2.CEM.TK	CC50 CEM	CEM/EC50 MSV	MC/CC50 MSV
1217	HWT	OH	CaproylNH	-	T						1.4	
1218	PS	PhO	PtAlaNH	-	T						<0.08	
1219	PS	PhO	neoPntAlaNH	-	T						<0.08	
1220	PS	PhO	PhenethylAlaN	-	T						0.7	
1224	HWT	OH	Me-GABA-NH	-	T						1	
1225	PS	PhO	1-NaphthMethAla	-	T						<0.08	
1227	PS	PhO	2-NaphthMethAla	-	T						<0.08	

TABLE 6 (CONT'D.)

Prod	Init	AO	Y	Z	B	HIV1 MI	HIV2 MI	MCC50 M	HIV1 CEM	HIV2 CEM	EC50 CEM	EC50 MSV	MCCMSV
462	PB	PhO	MeAlaNH	N3-up	T	3.3	11	121	27.5	40	30		
499	PB	-		N3-up	T	0.9	2.3	>250	3	4	>250		
536	PB	mC5PhO	MeAlaNH	N3-up	T	0.45	0.9	104	1	2	3		
550	PB	3,5Cl2PhO	MeAlaNH	N3-up	T	0.5	1	98	1.4	3	12		
569	PB	-		N3-up	U			>400	>400	>400			
571	PB	PhO	MeAlaNH	N3-up	U			>202	>202	117			
657	ASS	PhO	HexNH	N3-up	T			>40	>40	>18			
659	ASS	PhO	BuNH	N3-up	T			>42	>42	>42			
661	ASS	PhO	C12NH	N3-up	T			>7	>7	>7			
687	DC	-		N3-up	BzI			2.5	2.8	>100	>100		
731	DC	PhO	BzAlaNH	N3-up	T			0.28	0.7	1.1	88		
739	DC	MeO	MeAlaNH	N3-up	T			10	18	>250	>250		
774	ASS	PhO	MeAlaNH	N3-up	N-OctI			>10	>10			15	
777	DC	2,4-Bz2PhO	MeAlaNH	N3-up	T			0.5	0.55	0.19	55		
780	DC	F5PhO	MeAlaNH	N3-up	T			23	33	100	106		
846	ASS	PhO	CNEO	N3-up	1			13	14	>250	>250		
847	ASS	TFEO	CNEO	N3-up	1			12	9	>250	>250		
850	ASS	PhO	OH	N3-up	1			18	9	>250	>250		
855	ASS	TFEO	OH	N3-up	1			17.5	17.5	>250	>250		
856	ASS	HexO	CNEO	N3-up	1			13	25	>250	>250		
857	ASS	HaxO	OH	N3-up	T			5	10	>250	>250		
941	ASS	PhO	Me-D-PheNH	N3-up				>50	>50				
1069	OW	-		H	A			4	8	17.5	>250	24.3	>100
1071	ASS	HO	HOC(O)AlaNH	N3-up	T			115	100	250	>250	>100	
1093	OW	PhO	MeAlaNH	H	A			0.016	0.035	0.055	2.57	1.95	>20
1221	CY	PhO	MeAlaNH	H	C			0.6					
1225	OW	PhO	MeAlaNH	H	T			1.2					

TABLE 7

In vivo TestingInhibitory effects of test compounds on the initiation of MSV-5 induced tumour formation in NRMI mice and on the survival of MSV inoculated NMRI mice.

Mice infected with Moloney Sarcoma Virus [MSV] were treated daily with either placebo, or d4T [at one of two doses] or with 10 compound 324 at one of the same [equi-molar] doses.

Two- to three-day old NMRI mice (weighing ~ 2 gram) were inoculated subcutaneously (s.c.) in the left hind leg with 50 μ l MSV (100 foci forming units, as measured by in vitro 15 determination of the virus-induced transformation of murine C3H embryo fibroblast cells). At 4 to 5 days post-infection, tumours develop and rapidly increase in volume upon further aging of the mice. Within 10 to 12 days post-infection, mice (then weighing ~ 5 to 6 gram) die from the viral infection. 20 Drug treatment started 1 hour prior to infection of the virus, and further compound administration was given daily i.p. for an additional 3 days. The mean day of tumour initiation (\pm standard deviation) and the mean day of survival of the mice (\pm standard deviation) was calculated and statistical 25 significance of the average delay of tumour formation and the mean day of survival in the treated groups versus the untreated (control) group was assessed by two-tailed student's t-test.

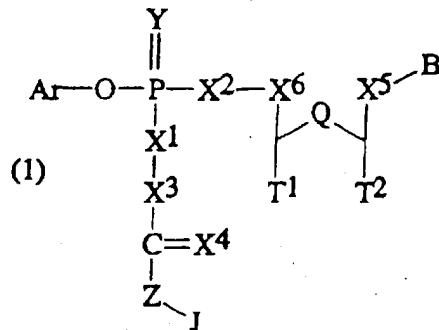
Whilst d4T failed to give any detectable delay in either tumour 30 appearance or death, a significant effect on both parameters was seen with high-dose compound 324, and an effect on the first disease parameter at low dose [Figure 1].

CLAIMS:

1. A compound of the formula (1)

5

10



15 wherein Ar is an aryl group;

Y is oxygen or sulphur;

20 X¹ is selected from O, NR³, S, CR³R⁴, CR³W¹ and CW¹W² where R³ and R⁴ are independently selected from hydrogen, alkyl and aryl groups; and W¹ and W² are heteroatoms;

25 X²-X⁶ may be absent; or X⁶ is CH₂ and X² is selected (independently of X¹) from O, NR³, S, CR³R⁴, CR³W¹ and CW¹W² where R³ and R⁴ are independently selected from hydrogen, alkyl and aryl groups; and W¹ and W² are heteroatoms;

30 X³ is a C₁₋₆ alkyl group;

X⁴ is oxygen or CH₂;

X⁵ may be absent or is CH₂;

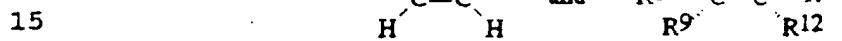
35

Z is selected from O, NR⁵, S, alkyl and aryl groups, where R⁵ is selected from hydrogen, alkyl and aryl groups;

J is selected from hydrogen, alkyl, aryl, heterocyclic and polycyclic groups;

5 Q is selected from O, NR⁶, S, CR⁶R⁷, CR⁶W³ and CW³W⁴ where R⁶ and R⁷ are independently selected from hydrogen, alkyl and aryl groups; and W³ and W⁴ are heteroatoms;

10 T¹ and T² are independently selected from hydrogen and CH₂R⁸, where R⁸ is selected from H, OH and F; or T¹ and T² are linked together and together are selected from the groups



20 20 where R⁹ is selected from H, halogen, CN, NH₂, CO-alkyl and alkyl; and R¹⁰, R¹¹ and R¹² are independently selected from H, N₃, halogen, CN, NH₂, CO-alkyl and alkyl;

B is a purine or pyrimidine base;

25 or a pharmaceutically acceptable derivative or metabolite thereof.

2. A compound according to claim 1 wherein

30 Y is oxygen;

X¹ is NH;

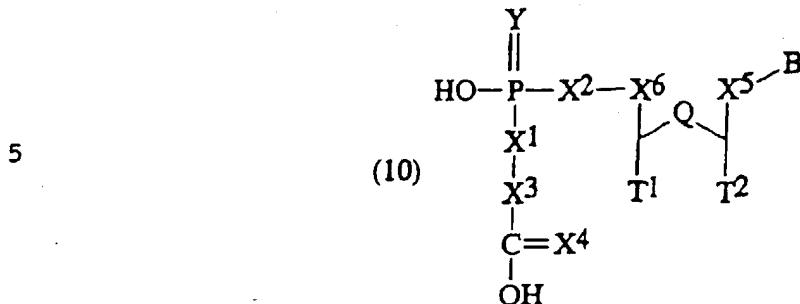
X³ is CHR¹;

X⁴ is oxygen; and

Z is oxygen.

35

3. A compound of formula (10)



10 or pharmaceutically acceptable derivative or metabolite thereof.

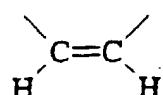
4. A compound according to claim 3 wherein

15 Y is oxygen;
 X¹ is NH;
 X³ is CHR¹; and
 X⁴ is oxygen

20 5. A compound according to any one of claims 1 to 4 wherein

25 X² is oxygen;
 X⁶ is CH₂;
 Q is oxygen;
 X⁵ is absent; and
 T¹ and T² together comprise the group:-

30



35 6. A compound according to claim 5 wherein B is thymine.

7. A compound according to claim 6 wherein Ar, R¹ and J are defined as follows:-

Compound Reference	Ar	R ¹	J
323	4-EtPh	Me	Me
324	Ph	Me	Me
5 327	4-FPh	Me	Me
526	3-CF ₃ Ph	Me	Me
546	3, 5-Cl ₂ Ph	Me	Me
730	Ph	Me	Bzl
776	2, 4-Br ₂ Ph	Me	Me
10 779	F ₃ Ph	Me	Me
862	Ph	Me	Hexyl
863	Ph	Bzl	Me
864	Ph	CH ₂ iPr	Me
865	Ph	iPr	Me
15 866	Ph	H	Me
867	Ph	[CH ₂] ₂ SMe	Me
868	2, 4Br ₂ Ph	Me	Bzl
877	Ph	Bzl	Bzl
878	Ph	Bzl	tBu
20 892	Ph	Me	Cyclohexyl
893	Ph	Me	tBu
1078	Ph	CH ₃ CO ₂ H	Me
1214	Ph	CH ₃ CH ₂ CH ₂ NHC[NH ₂] NH	Me
1218	Ph	Me	n-Pent
25 1219	Ph	Me	neo-Pent
1225	Ph	Me	1-Naphthyl
1227	Ph	Me	2-Naphthyl

30 8. A compound according to any one of claims 1 to 4
wherein

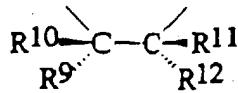
X² is oxygen;

X⁶ is CH₂;

Q is oxygen;

35 X⁵ is absent; and

T¹ and T² together comprise the group:-



9. A compound according to claim 8 wherein B is adenine or thymine.

10. A compound according to any one of claims 1 to 4 wherein
5 X^2-X^6 is absent

Q is oxygen;

X^5 is CH_2 ;

T^1 and T^2 are independently selected from hydrogen and CH_2R^8 wherein R^8 is selected from H, OH and F.

10

11. A compound according to claim 9 wherein B is adenine.

12. A compound according to any one of claims 1 to 11 for use in a method of treatment, prophylaxis or diagnosis.

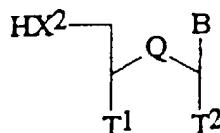
15

13. Use of a compound according to any one of claims 1 to 11 in the manufacture of a medicament for the treatment or prophylaxis of a viral infection.

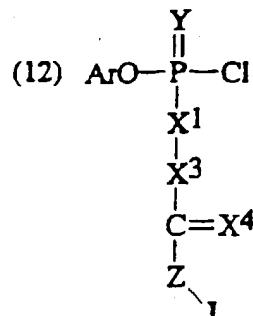
20 14. Use of a compound according to claim 13 wherein the viral infection comprises HIV.

15. A process for the preparation of a compound according to any one of claims 1 to 11 comprising reaction of a compound
25 of formula (11)

30



35 with a compound of formula (12)



10 16. A method of prophylaxis or treatment of viral infection comprising administration to a patient in need of such treatment an effective dose of a compound according to any one of claims 1 to 11.

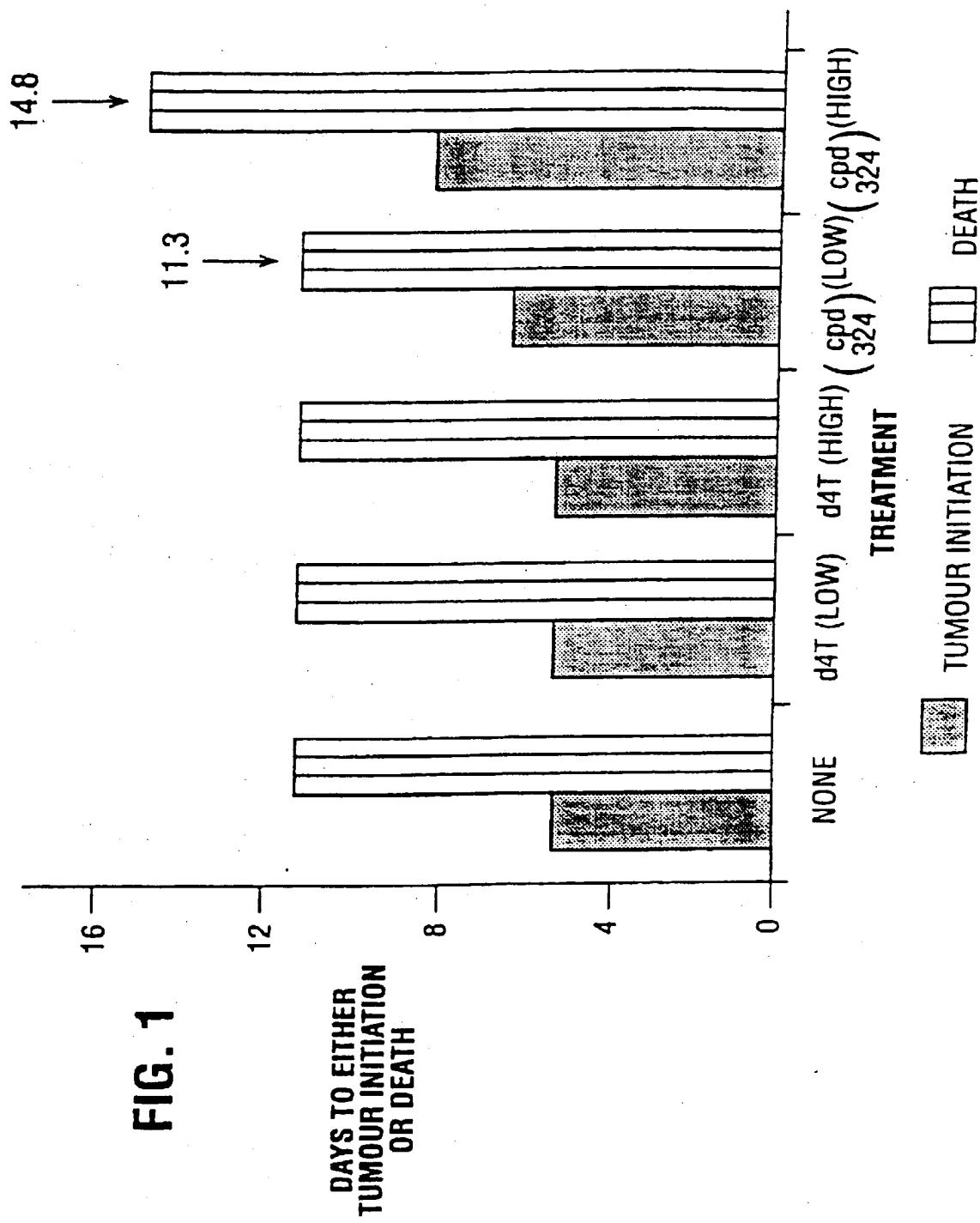
15 17. Use of a compound according to any one of claims 1 to 11 in the manufacture of a medicament for use in the inhibition of a reverse transcriptase by a nucleoside-resistance independent or nucleoside 5'-triphosphate independent mode of action.

20

18. A pharmaceutical composition comprising a compound according to any one of claims 1 to 11 in combination with a pharmaceutically acceptable excipient.

25

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/NL/6/00580

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07H19/10 C07H19/20 A61K31/70 C07F9/6512 C07F9/6524
A61K31/675

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07H A61K C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>FEBS LETTERS, vol. 351, no. 1, 1994, AMSTERDAM NL, pages 11-14, XP000578147</p> <p>MCGUIGAN, CHRISTOPHER ET AL: "Certain phosphoramidate derivatives of dideoxy uridine (ddU) are active against HIV and successfully bypass thymidine kinase" see the whole document</p> <p>---</p>	1,2,8, 12-18
X	<p>JOURNAL OF MEDICINAL CHEMISTRY, vol. 36, no. 8, 1993, pages 1048-1052, XP000578135</p> <p>MCGUIGAN, CHRISTOPHER ET AL: "Intracellular delivery of bioactive AZT nucleotides by aryl phosphate derivatives of AZT" cited in the application see the whole document</p> <p>---</p> <p>-/-</p>	1,2,8,9, 12-18

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

& document member of the same patent family

2

Date of the actual completion of the international search	Date of mailing of the international search report
14 August 1996	04-09-1996
Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentstaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl. Fax (+ 31-70) 340-3016	Day, G

INT'L. TIONAL SEARCH REPORT

Int'l Application No.
PCT/US 96/00580

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 2, no. 7, 1992, OXFORD, UK, pages 701-704, XP000578777 MC GUIGAN C ET AL: "Aryl phosphate derivatives of AZT inhibit HIV replication in cells where the nucleoside is poorly active" see the whole document ---	1,2,8,9, 12-18
X	ANTIVIRAL RESEARCH, vol. 17, no. 4, 1992, pages 311-321, XP000578782 MC GUIGAN C ET AL: "Aryl phosphates derivatives of AZT retain activity against HIV1 in cell lines which are resistant to the action of AZT" see the whole document ---	1,2,8,9, 12-18
P,X	ANTIVIRAL CHEMISTRY & CHEMOTHERAPY, vol. 7, no. 1, 1996, pages 31-36, XP000578787 MC GUIGAN C ET AL: "Phosphoramidates as potent prodrugs of anti-HIV nucleotides: studies in the amino region" see the whole document ---	1,2,5-7, 12-18
A	JOURNAL OF MEDICINAL CHEMISTRY, vol. 37, no. 21, 1994, pages 3534-3541, XP000578132 FRANCHETTI P ET AL: "Synthesis and Evaluation of the Anti-HIV Activity of Aza and Deaza Analogs of IsoddA and Their Phosphates as Prodrugs" see page 3537 ---	1,12-18
A	JOURNAL OF MEDICINAL CHEMISTRY, vol. 37, no. 12, 10 June 1994, pages 1857-1864, XP000564485 STARRETT J E ET AL: "SYNTHESIS, ORAL BIOAVAILABILITY DETERMINATION, AND IN VITRO EVALUATION OF PRODRUGS OF THE ANTIVIRAL AGENT 3- 2-(PHOSPHONOMETHOXY) ETHYLADENINE (PMEA)" see page 1858 -----	10,11

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB96/00580

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:

because they relate to subject matter not required to be searched by this Authority, namely:

Remark : Although claim 16 is directed to the treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds (rule 39.1 (iv) PCT).

2. Claims Nos.:

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claims Nos.:

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, thus Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.